California Health Benefits Review Program

Analysis of California Senate Bill 746
Anticancer Medical Devices

A Report to the 2019-2020 California State Legislature April 19, 2019

Key Findings:

Analysis of California Senate Bill 746 Anticancer Medical Devices

Summary to the 2019–2020 California State Legislature, April 19, 2019

CALIFORNIA HEALTH BENEFITS REVIEW PROGRAM

AT A GLANCE

The version of California Senate Bill (SB) 746 analyzed by CHBRP would require that health plans and policies effective on or after January 1, 2020, that cover chemotherapy or radiation therapy for the treatment of cancer also cover anticancer medical devices that meet definitions set forth in SB 746.

1. CHBRP estimates that, in 2020, all of the 24.5 million Californians enrolled in state-regulated health insurance will have insurance subject to SB 746.
2. **Benefit coverage.** Among enrollees that would be subject to SB 746, 91% have coverage for anticancer medical devices, which are categorized by health plans as durable medical equipment (DME). Because DME is already a covered benefit under California's definition of essential health benefits (EHBs), SB 746 would not require coverage for a new state benefit mandate that appears to exceed the definition of EHBs.
3. **Utilization.** It is estimated that there will be 56 adult enrollees with coverage subject to SB 746 using Optune® in the baseline year, and that utilization may increase by 10% (five users) postmandate.
4. **Expenditures.** The cost of Optune® is $21,000 per user per month, and the average length of use is 5.2 months. It is estimated that SB 746 would increase total net annual expenditures by $648,000 or 0.0004%.
5. **Medical effectiveness.** Adults with glioblastoma multiforme (GBM) using Optune® have increased overall survival and progression-free survival.
6. **Public health.** There is no projected measurable public health impact at the population level due to the small estimated increase in utilization.
7. **Long-term impacts.** The potential long-term impacts of SB 746 are unknown; larger impacts may occur in the long-term as more patients use the device and if the FDA approves more devices that are effective at treating cancer.

[1] Refer to CHBRP's full report for full citations and references.

CONTEXT

CHBRP has identified only one anticancer medical device that meets the definitions in SB 746. This is based on CHBRP's review of the literature as well as consultation with experts at the FDA and academic institutions. This device is known as Optune® and is used in the treatment of a type of brain cancer called glioblastoma multiforme (GBM). This device was approved by the FDA to treat patients with recurrent GBM in 2011 and patients newly diagnosed with GBM in 2015.[1]

Cancers of the brain and central nervous system (CNS) make up 1.35% of all cancers. GBM is the third most common of all brain and CNS tumors (14.7%) and accounts for 47.7% of malignant brain tumors. It is estimated that 2,530 new cases of brain and CNS cancer cases will be diagnosed in California in 2019, and of these, approximately 1,200 (47.7%) are GBM. The 5-year survival rate for those diagnosed with GBM is the lowest of any cancer of the brain or CNS at approximately 5.6%.

CHBRP's analysis discusses the impact of mandating coverage for Optune®, which is a battery-operated, wearable, portable device that uses four adhesive patches to deliver low-intensity tumor treating fields (TTFields) to the GBM tumor. These patches are connected to the device and applied to the patient's scalp. Although it is possible that other devices will be covered in the future, or that Optune® will be approved for the treatment of other types of cancer, for this analysis, CHBRP only describes current FDA-approved (as of March 2019) anticancer medical devices.

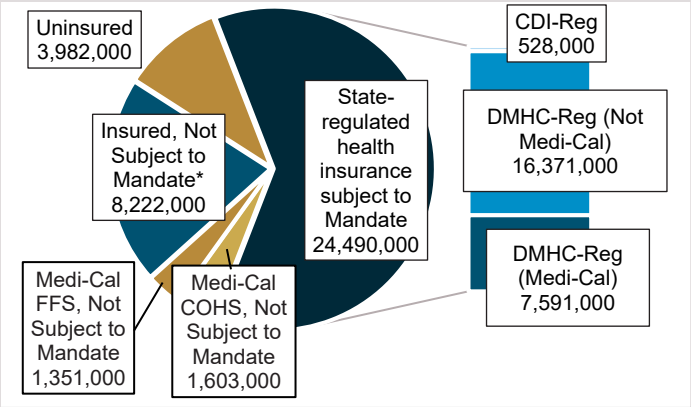
CHBRP has assumed that SB 746 would be applicable to all health plans regulated by the California Department of Managed Health Care (DMHC) (including Medi-Cal Managed Care Plans) and policies regulated by the California Department of Insurance (CDI) as of January 1, 2020.

BILL SUMMARY

SB 746 would require that health plans and policies effective on or after January 1, 2020, that cover chemotherapy or radiation therapy for the treatment of cancer also cover anticancer medical devices. The bill requires coverage of these medical devices only when the device has been approved by the FDA, is designed for use outside of a treatment facility, and is prescribed for the treatment of cancer based on medical necessity.

Figure A shows how many Californians have health insurance that would be subject to SB 746.

Figure A. Health Insurance in CA and SB 746



Source: California Health Benefits Review Program, 2019.
Notes: *Medicare beneficiaries, enrollees in self-insured products, etc.

IMPACTS

Benefit Coverage, Utilization, and Cost

As noted above, this analysis focused on the use of Optune® to treat GBM because it is the only anticancer device on the market today that meets the specifications of SB 746. According to the bill, "anticancer medical device" means a medical device, including component parts, services, and supplies necessary for the effective use of the device.

Benefit Coverage

Among current enrollees with health insurance that would be subject to SB 746, 91% have coverage for Optune®, as determined by a survey of the largest (by enrollment) providers of health insurance in California. Responses to this survey represent 82% of enrollees with private market health insurance that can be subject to state mandates.

Health plans and policies that cover Optune® do so under the durable medical equipment (DME) benefit, and any cost-sharing requirements for DME, such as deductibles, copayments, and coinsurance, apply to Optune®.

Utilization

It is estimated that there will be 1,200 new cases (3.21 cases per 100,000 people) of GBM in California each year, with about 50% among adults aged 65 and over. SB 746 would not affect coverage for most older adults with GBM because most have coverage through the Medicare program, which is not subject to state benefit mandates.

Based on the age-adjusted incidence rate, CHBRP estimated that there will be 56 adult enrollees with coverage subject to SB 746 using Optune® in the baseline year. Even with insurance coverage for Optune®, patients may decide not to use it due to a variety of factors (e.g., not wanting to shave their head or wear a visible device, incompatibility with continuing to work), or providers may not offer it as a potential treatment.

Patients who live longer due to the use of Optune® may incur use of other services (e.g., chemotherapy), but CHBRP did not include those in the utilization and cost impact estimates due to limitations of current claims data.

Postmandate, it is estimated that the utilization of Optune® may increase 10% due to increased awareness and acceptance of the treatment by both providers and patients, which would result in five more users.

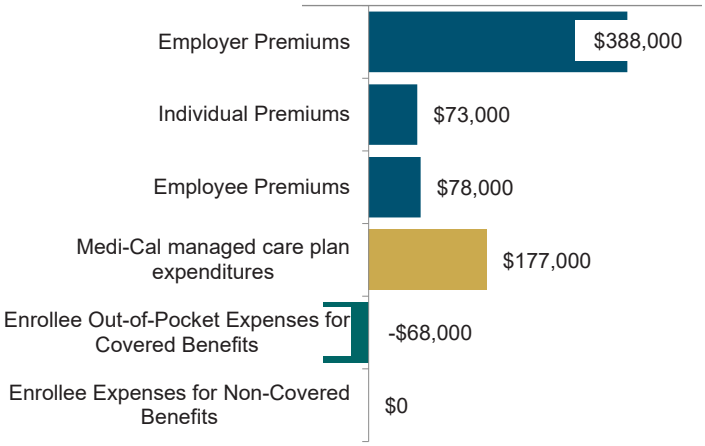
Expenditures

The cost of Optune® is $21,000, with an average cost paid by health plans and insurers of $18,624 per month per user, which includes component parts, services, and supplies necessary for the effective use of the device. The average length of Optune® use is 5.2 months. CHBRP estimates the average cost will be $96,845 per user. SB 746 would increase total net annual expenditures by $648,000 or 0.0004%. This is due to a $717,000 increase in total health insurance premiums paid by employers and enrollees for newly covered benefits, adjusted by an increase in enrollee expenses for covered and/or noncovered benefits. CHBRP projects no change to copayments or coinsurance for those with coverage but

does project an increase in the utilization of Optune® and therefore an increase in overall enrollee cost sharing. Expenditure impacts are shown in Figure B.

CHBRP does not project any cost offsets or savings in health care that would result postmandate since Optune® is used to complement other standard treatments.

Figure B. Expenditure Impacts of SB 746



Source: California Health Benefits Review Program, 2019.

Medi-Cal

CHBRP estimates there will be a $177,000 increase in expenditures for the 7.6 million Medi-Cal beneficiaries enrolled in DMHC-regulated plans.

CalPERS

CHBRP does not expect the impacts for CalPERS enrollees to be different from those for enrollees in other plans or policies.

Number of Uninsured in California

Because the change in average premiums does not exceed 1% for any market segment, CHBRP expects no measurable change in the number of uninsured persons due to the enactment of SB 746.

Medical Effectiveness

CHBRP's review of the literature focused on the following outcomes: (1) overall survival, (2) progression-free survival, (3) quality of life and functional status, and (4) harms from the treatment.

CHBRP found a preponderance of evidence that adults with GBM receiving Optune® have increased overall survival (i.e., the length of time during which the GBM does not get worse) compared to those who receive standard care (e.g., active chemotherapy such as temozolomide [TMZ]). There is limited evidence that Optune® increases progression-free survival among people with newly diagnosed GBM. Findings regarding the effects of Optune® on functional status and quality of life are inconclusive. There is limited evidence that using Optune® does not lead to more frequent or severe harms than standard of care; skin irritation or reaction was the most common harm identified.

Public Health

Despite a preponderance of evidence that Optune® is medically effective, CHBRP projects no measurable public health impact at the population level due to the small estimated increase in utilization (i.e., five new users). However, SB 746 would likely yield increased length of life among the additional five enrollees who would use Optune® in the treatment of GBM.

Racial or ethnic disparities in the prevalence and treatment of GBM exist; however, CHBRP did not find evidence to suggest that SB 746 would impact utilization of Optune® differentially by race or ethnicity. Therefore, CHBRP projects no impact on racial or ethnic disparities related to GBM treatment and survival.

Long-Term Impacts

After the estimated increase in utilization in the first 12 months, there is no indication in the research literature that the trend of utilization and incidence rate of enrollees with GBM will change over time. Because of this, CHBRP assumes that the 10% increase projected for Year 1 will persist in Year 2. However, in the long term, it is possible that Optune® could be improved and be utilized more widely as the treatment becomes more normalized and patient acceptance increases.

There are several preliminary studies underway that assess the efficacy and safety of Optune® for other conditions and populations such as pediatric GBM, non-small cell lung cancer, pancreatic cancer, ovarian cancer,

and cancer that has metastasized in the brain from other locations. It is uncertain what impact Optune® could have on survival rates for these cancers. There also may be more anticancer medical devices that come to the market in the future. If either of these things happens, the overall utilization of anticancer devices will increase, along with cost.

The potential long-term impact of SB 746 is unknown, although it stands to reason that there is the potential for a larger impact in the long-term if the FDA approves Optune® to treat other cancers or approves other anticancer medical devices that are effective at treating cancer.

Essential Health Benefits (EHBs) and the Affordable Care Act

Anticancer medical devices are categorized by health plans as durable medical equipment (DME). Because DME is already a covered benefit under California's definition of EHBs, SB 746 would not require coverage for a new state benefit mandate that appears to exceed the definition of EHBs.

A Report to the California State Legislature

Analysis of California Senate Bill 746
Anticancer Medical Devices

April 19, 2019

California Health Benefits Review Program
MC 3116; Berkeley, CA 94720-3116
www.chbrp.org

The California Health Benefits Review Program (CHBRP) was established in 2002. As per its authorizing statute, CHBRP provides the California Legislature with independent analysis of the medical, financial, and public health impacts of proposed health insurance benefit-related legislation. The state funds CHBRP through an annual assessment on health plans and insurers in California.

An analytic staff based at the University of California, Berkeley, supports a task force of faculty and research staff from multiple University of California campuses to complete each CHBRP analysis. A strict conflict-of-interest policy ensures that the analyses are undertaken without bias. A certified, independent actuary helps to estimate the financial impact. Content experts with comprehensive subject-matter expertise are consulted to provide essential background and input on the analytic approach for each report.

More detailed information on CHBRP's analysis methodology, authorizing statute, as well as all CHBRP reports and other publications are available at www.chbrp.org.

TABLE OF CONTENTS

List of Tables and Figures viii
Policy Context 1
Bill-Specific Analysis of SB 746, Anticancer Medical Devices 1
Interaction With Existing Requirements 1
Analytic Approach and Key Assumptions 3
Background on Cancer, Glioblastoma, and Related Treatments 4
Cancer 4
Glioblastoma Multiforme (GBM) 4
Treatment of GBM 5
Disparities and Social Determinants of Health in Cancer Treatment 7
Medical Effectiveness 9
Research Approach and Methods 9
Methodological Considerations 10
Outcomes Assessed 11
Study Findings 11
Benefit Coverage, Utilization, and Cost Impacts 16
Key Assumptions 16
Baseline and Postmandate Benefit Coverage 16
Baseline and Postmandate Utilization 16
Baseline and Postmandate Per-Unit Cost 17
Baseline and Postmandate Expenditures 17
Other Considerations for Policymakers 19
Public Health Impacts 24
Estimated Public Health Outcomes 24
Impact on Disparities 24
Long-Term Impacts 26
Long-Term Utilization and Cost Impacts 26
Long-Term Public Health Impacts 26
Appendix A Text of Bill Analyzed A-1
Appendix B Literature Review Methods B-1
Appendix C Cost Impact Analysis: Data Sources, Caveats, and Assumptions C-1
Appendix D Information Submitted by Outside Parties D-1
References
California Health Benefits Review Program Committees and Staff

LIST OF TABLES AND FIGURES

Table 1. SB 746 Impacts on Benefit Coverage, Utilization, and Cost, 2020 ix

Table 2. Incidence and 5-Year Survival Rates for GBM by Gender, Race, Age at Diagnosis and Location, United States 6

Table 3. Key Attributes of Studies Included in the Medical Effectiveness Review 10

Table 4. Baseline Per Member Per Month Premiums and Total Expenditures by Market Segment, California, 2020 20

Table 5. Postmandate Per Member Per Month Premiums and Total Expenditures by Market Segment, California, 2020 22

Table 6. Optune® Utilization and Cost (2016 CHSD and MarketScan) C-2

Table 7. SB 746 Impacts on Benefit Coverage, Utilization, and Cost, 2021 ..... C-4

Figure 1. Optune® Device by Novocure 6

Figure 2. Effect of Optune® on Median Overall Survival Among Adults with GBM 13

Figure 3. Effect of Optune® on Median Progression-Free Survival Among Adults with Newly Diagnosed GBM 14

Figure 4. Effect of Optune® on Quality of Life and Functional Status 14

Figure 5. Harms of Optune® 15

Table 1. SB 746 Impacts on Benefit Coverage, Utilization, and Cost, 2020

	Baseline	Postmandate	Increase/ Decrease	Change Postmandate
Benefit Coverage				
Total enrollees with health insurance subject to state-level benefit mandates (a)	24,490,000	24,490,000	0	0%
Total enrollees with health insurance subject to SB 746	24,490,000	24,490,000	0	0%
Percentage of enrollees with coverage for anti-cancer medical devices	91%	100%	9%	10%
Utilization and Cost				
Utilization per 1,000	0.012	0.013	0.001	10%
Total enrollees subject to SB 746 using anti-cancer medical devices	56	61	5	9%
Average cost per enrollee using anti-cancer medical devices	96,845	96,845	0.00	0%
Expenditures				
Premium expenditures by payer				
Private employers for group insurance	$86,438,375,000	$86,438,752,000	$377,000	0.0004%
CalPERS HMO employer expenditures (c)	$3,098,551,000	$3,098,562,000	$11,000	0.0004%
Medi-Cal Managed Care Plan expenditures (d)	$28,492,273,000	$28,492,450,000	$177,000	0.0006%
Enrollees for individually purchased insurance	$12,045,324,000	$12,045,397,000	$73,000	0.0006%
Individually purchased – outside exchange	$2,486,222,000	$2,486,234,000	$12,000	0.0005%
Individually purchased – Covered California	$9,559,102,000	$9,559,163,000	$61,000	0.0006%
Enrollees with group insurance, CalPERS HMOs, Covered California, and Medi-Cal Managed Care (a) (b)	$14,476,394,000	$14,476,472,000	$78,000	0.0005%
Enrollee expenses				
Enrollee out-of-pocket expenses for covered benefits (deductibles, copayments, etc.)	$14,750,880,000	$14,750,812,000	-$68,000	-0.0005%
Enrollee expenses for noncovered benefits (e)	$0	$0	$0	0.00%
Total Expenditures	$159,301,797,000	$159,302,445,000	$648,000	0.0004%

Source: California Health Benefits Review Program, 2019.

Notes: (a) Enrollees in plans and policies regulated by DMHC or CDI aged 0 to 64 years as well as enrollees 65 years or older in employer-sponsored health insurance. This group includes commercial enrollees (including those associated with Covered California or CalPERS) and Medi-Cal beneficiaries enrolled in DMHC-regulated plans.[2]

(b) Approximately 56.17% of CalPERS enrollees in DMHC-regulated plans are state retirees, state employees, or their dependents. About one in five (20.5%) of these enrollees has a pharmacy benefit not subject to DMHC.[3] CHBRP has projected no impact for those enrollees. However, CalPERS could, postmandate, require equivalent coverage for all its members (which could increase the total impact on CalPERS).

(c) Enrollee premium expenditures include contributions by employees to employer-sponsored health insurance, health insurance purchased through Covered California, and contributions to Medi-Cal Managed Care.

(d) Includes only expenses paid directly by enrollees (or other sources) to providers for services related to the mandated benefit that are not currently covered by insurance. This only includes those expenses that would be newly covered postmandate. Other components of expenditures in this table include all health care services covered by insurance.

(e) Although enrollees with newly compliant benefit coverage may have paid for some Optune® use before SB 746, CHBRP cannot estimate the frequency with which such situations may have occurred and therefore cannot estimate the related expense. Postmandate, such expenses would be eliminated, though enrollees with newly compliant benefit coverage might, postmandate, pay for some [tests/treatments/services] for which coverage is denied (through utilization management review), as some enrollees who always had compliant benefit coverage may have done and may continue to do, postmandate.

Key: CalPERS = California Public Employees' Retirement System; CDI = California Department of Insurance; DMHC = Department of Managed Health Care; HMO = Health Maintenance Organizations

[2] For more detail, see *Estimates of Sources of Health Insurance in California*, available at http://chbrp.com/analysis_methodology/cost_impact_analysis.php.

[3] For more detail, see *Estimates of Pharmacy Benefit Coverage*, available at http://chbrp.com/analysis_methodology/cost_impact_analysis.php).

POLICY CONTEXT

The California Senate Committee on Health has requested that the California Health Benefits Review Program (CHBRP)[4] conduct an evidence-based assessment of the medical, financial, and public health impacts of Senate Bill (SB) 746, Anticancer Medical Devices.

Bill-Specific Analysis of SB 746, Anticancer Medical Devices

Bill Language Summary

SB 746 would require that health plans and policies effective on or after January 1, 2020, that cover chemotherapy or radiation therapy for the treatment of cancer also cover anticancer medical devices. It requires coverage of these medical devices only when the device has been approved by the FDA, is designed for use outside of a treatment facility, and is prescribed for the treatment of cancer based on medical necessity. The full text of SB 746 can be found in Appendix A.

Relevant Populations

If enacted, SB 746 would affect the health insurance of approximately 24.5 million enrollees (61.8% of all Californians). This represents 100% of the 24.5 million Californians who will have health insurance regulated by the state that may be subject to any state health benefit mandate law — health insurance regulated by the California Department of Managed Health Care (DMHC) or the California Department of Insurance (CDI). This includes Medi-Cal Managed Care Plan (MCP) enrollees.

Interaction With Existing Requirements

Health benefit mandates may interact and align with the following state and federal mandates or provisions.

California Policy Landscape

California law and regulations

Cancer-related mandates

There are currently seven state benefit mandates[5] that require screening, diagnosis, and/or treatment for cancer. These include:

- Breast cancer screening, diagnosis, and treatment;[6]
- Cancer screening tests;[7]

[4] CHBRP's authorizing statute is available at http://www.chbrp.org/about_chbrp/index.php.
[5] A list of current health insurance benefit mandates in California state and Federal law is available under "Resources" at http://chbrp.com/other_publications/index.php.
[6] California Health and Safety Code 1367.6; California Insurance Code 10123.8.
[7] California Health and Safety Code 1367.665; California Insurance Code 10123.20.

- Cervical cancer screening;[8]
- Mammography;[9]
- Mastectomy and lymph node dissection (length of stay, complications, prostheses, reconstructive surgery);[10]
- Patient care related to clinical trials for cancer;[11] and
- Prostate cancer screening.[12]

SB 746 is not expected to interact with any of these mandates in the immediate future, since the only anticancer medical device identified by CHBRP at this time is for the treatment of a type of brain cancer, glioblastoma multiforme (GBM), which is not included in any of the above mandates.

Through surveys and queries, CHBRP found that California health plans and insurers consider anticancer medical devices to fall under the durable medical equipment (DME) category. DME is defined as "equipment and supplies ordered by a health care provider for everyday or extended use."[13] CHBRP is not aware of any current or proposed benefit mandates related to DME.

Similar requirements in other states

CHBRP is not aware of similar benefit mandates in any other states related to anticancer medical devices.

Federal Policy Landscape

Affordable Care Act

Essential Health Benefits

State health insurance marketplaces, such as Covered California, are responsible for certifying and selling qualified health plans (QHPs) in the small-group and individual markets. QHPs are required to meet a minimum standard of benefits as defined by the ACA as essential health benefits (EHBs). In California, EHBs are related to the benefit coverage available in the Kaiser Foundation Health Plan Small Group Health Maintenance Organization (HMO) 30 plan, the state's benchmark plan for federal EHBs.[14,15]

[8] California Health and Safety Code 1367.66; California Insurance Code 10123.18.
[9] California Health and Safety Code 1367.65; California Insurance Code 10123.81.
[10] California Health and Safety Code 1367.635; California Insurance Code 10123.86.
[11] California Health and Safety Code 1370.6; California Insurance Code 10145.4.
[12] California Health and Safety Code 1367.64; California Insurance Code 10123.835.
[13] This definition of DME is available at http://www.healthcare.gov/glossary.
[14] The U.S. Department of Health and Human Services (HHS) has allowed each state to define its own EHBs for 2014 and 2015 by selecting one of a set of specified benchmark plan options. CCIIO, Information on Essential Health Benefits Benchmark Plans. Available at: https://www.cms.gov/cciio/resources/data-resources/ehb.html.
[15] H&SC Section 1367.005; IC Section 10112.27.

California's benchmark plan includes coverage for DME for home use and requires prior authorization for coverage.[16] However, only about 5.1 million Californians are enrolled in a health plan or policy that is subject to EHBs.[17] States may require QHPs to offer benefits that exceed EHBs.[18] However, a state that chooses to do so must make payments to defray the cost of those additionally mandated benefits, either by paying the purchaser directly or by paying the QHP.[19,20] State rules related to provider types, cost-sharing, or reimbursement methods would *not meet* the definition of state benefit mandates that could exceed EHBs.[21]

SB 746 would not require coverage for a new state benefit mandate that appears to exceed the definition of EHBs in California, since anticancer medical devices are categorized by health plans as DME, and DME is already a covered benefit under California's definition of EHBs.

Analytic Approach and Key Assumptions

For the purposes of this analysis, CHBRP has assumed that there is only one anticancer medical device that meets the definitions in SB 746. This is based on CHBRP's review of the literature as well as consultation with an expert at the FDA.[22] This device is known as Optune® and is used in the treatment of GBM. This device was first approved by the FDA to treat patients with recurrent GBM in 2011 and patients newly diagnosed with GBM in 2015.

This analysis will only discuss the impact of mandating coverage for Optune®.

For the purposes of this analysis, CHBRP has assumed that SB 746 would be applicable to all DMHC-regulated plans (including Medi-Cal Managed Care Plans) and CDI-regulated policies as of January 1, 2020.

[16] A summary of benchmark plan requirements in California is available at http://www.cms.gov/ccio/resources/data-resources/ehb.html.
[17] More information on California health insurance subject to EHBs is available in CHBRP's "Estimates of Sources of Health Insurance in California" document under "Resources" at http://www.chbrp.org/other_publications/index.php.
[18] ACA Section 1311(d)(3).
[19] State benefit mandates enacted on or before December 31, 2011, may be included in a state's EHBs, according to the U.S. Department of Health and Human Services (HHS). Patient Protection and Affordable Care Act: Standards Related to Essential Health Benefits, Actuarial Value, and Accreditation. Final Rule. Federal Register, Vol. 78, No. 37. February 25, 2013. Available at: www.gpo.gov\fdsys\pkg\FR-2013-02-25\pdf\2013-04084.pdf.
[20] However, as laid out in the Final Rule on EHBs HHS released in February 2013, state benefit mandates enacted on or before December 31, 2011, would be included in the state's EHBs and there would be no requirement that the state defray the costs of those state mandated benefits. For state benefit mandates enacted after December 31, 2011, that are identified as exceeding EHBs, the state would be required to defray the cost.
[21] Essential Health Benefits. Final Rule. A state's health insurance marketplace would be responsible for determining when a state benefit mandate exceeds EHBs, and QHP issuers would be responsible for calculating the cost that must be defrayed.
[22] Personal communication with Jonathan S. Helfgott, formerly the Associate Director for Risk Science, within the Office of Scientific Investigations at FDA's Center for Drug Evaluation & Research (CDER). Prior to joining CDER in 2010, Mr. Helfgott worked at the FDA's Center for Devices and Radiological Health (CDRH) within the Division of Bioresearch Monitoring (BIMO), March 2019.

BACKGROUND ON CANCER, GLIOBLASTOMA, AND RELATED TREATMENTS

SB 746 requires health insurance coverage for FDA-approved devices for the treatment of cancer. CHBRP's review of the literature as well as consultation with experts on FDA[23] protocol found that currently there is only one such device, Optune®, which is used in the treatment of a type of brain cancer called glioblastoma multiforme (GBM). For the purposes of this analysis, CHBRP will only discuss the impact of mandating coverage for Optune®. Although it is possible that other devices will be covered in the future, or that Optune® will be approved for the treatment of other types of cancer, this analysis only describes current FDA-approved (as of March 2019) anticancer devices.

This background section provides context for CHBRP's analysis of SB 746 by discussing the incidence of cancer overall and GBM specifically, treatment options, and barriers to treatment with Optune®, as well as the social determinants of health that may influence treatment in California. Note that the following discussion broadly applies to the general population and includes persons with insurance subject to SB 746 as well as the uninsured and those with health insurance not subject to state-regulated mandates, unless otherwise stated.

Cancer

Nearly one in two Californians born today will develop cancer at some point in his or her lifetime (CCR, 2017). The treatment options for cancer depend on the type of cancer, as well as the stage of diagnosis, and include surgical removal, radiation treatment, and medications, including chemotherapy. In California, an estimated 186,920 cases of cancer will be diagnosed in 2019, whereas approximately 1.5 million Californians alive today have a history with the disease (ACS, 2019; CCR, 2017). In California, cancer is the second leading cause of death, accounting for 23% of all deaths, or approximately 60,590 deaths in 2019 (ACS, 2017; ACS, 2019). Early diagnoses, through population-based screening, as well as advances in cancer treatment, have greatly improved survival rates of cancer patients (CCR, 2017). The 5-year cancer survival rate varies dramatically based on the type of cancer, with a high of 99% for prostate cancer and a low of 8% for pancreatic cancer (ACS, 2018).

Glioblastoma Multiforme (GBM)

Cancers of the brain and central nervous system (CNS) make up 1.35% of all cancers (ACS, 2019). GBM is the third most common of all brain and CNS tumors (14.7%) and accounts for 47.7% of malignant brain tumors (Ostrom et al., 2018). It is estimated that there will be 2,530 new cases of brain and CNS cancer cases diagnosed in California in 2019 (ACS, 2019). Of these, approximately 1,200 (47.7% of 2,530) are GBM (ACS, 2019; Ostrom et al., 2018).

The incidence rates for GBM for different groups in the United States are presented in Table 2. The overall annual adjusted incidence rate is 3.21 cases per 100,000 people (Ostrom et al., 2018). This differs by gender, where males have 1.58 times higher rates compared to females (Ostrom et al., 2018). Whites have the highest incidence rates compared to all other racial/ethnic groups. Incidence rates also increase with age, peaking in the 75–84 (15.13 per 100,000) and 65–74 (12.99 per 100,000) age groups. Those under age 20 had the lowest incidence rates (0.18 per 100,000) compared to all other age groups

[23] Personal communication with Jonathan S. Helfgott, March 2019.

(Ostrom et al., 2018; Killion et al., 2018). The median age of diagnosis is age 65, with 49% of the cases of GBM diagnosed prior to age 65 (Ostrom et al., 2018).

The 5-year survival rate for those diagnosed with GBM is the lowest of any cancer of the brain or CNS at approximately 5.6% (Ostrom et al., 2018). Table 2 also presents the overall 5-year survival rates for GBM for different demographic groups. While there were no differences in overall 5-year survival rates by gender, there were by age. Persons aged 0–19 and 20–44 had the highest survival rates (16.6% and 19.1% respectively) compared to all other age groups, with the 5-year survival rate declining significantly in each older age group. In addition, whites had lower 5-year survival rates compared to other racial and ethnic groups, and those living in rural areas had lower survival rates compared to those living in urban areas.

Treatment of GBM

Standard treatment for GBM has been surgery followed by radio-chemotherapy, a combination of radiation and chemotherapy treatments (Kinzel et al., 2019). This standard treatment regimen leads to an average survival of 15–17 months (Kinzel et al., 2019). A newer adjuvant treatment option known as tumor treating fields (TTFields) is now recommended as part of standard treatment by the National Comprehensive Cancer Network (NCCN) Guidelines (Kinzel et al., 2019). NCCN recommends that providers offer people with GBM the option to add TTFields to radiation therapy and chemotherapy treatment if they have a score ≥60 on the Karnofsky Performance Status scale, a standardized measure of the ability of cancer patients to perform activities of daily living (NCCN, 2018).

Optune® is the only TTFields device approved by the FDA to date. It is a battery-operated, wearable, and portable device that uses four adhesive patches to deliver low-intensity TTFields to the GBM tumor (see Figure 1). These patches are connected to the device and applied to the patient's scalp. It is recommended that the patient wear Optune® at least 75% of the time (i.e., 18 hours a day). The effectiveness of this treatment in improving survival rates and other outcomes related to GBM is discussed in the *Medical Effectiveness* section.

Figure 1. Optune® Device by Novocure

Source: https://www.harris.com/solution/cancer-treatment-with-novocure. Accessed on April 6, 2019.

In deciding whether to utilize the Optune® treatment as part of the overall GBM treatment strategy, patients consider factors related to disruptions in daily routine such as the requirement to keep your head shaved, visibility of the device, the time and caregiver effort required to change the patches connected to the scalp every 3 to 4 days, increased sweating in warm temperatures, and physical difficulty in carrying the device (Onken et al., 2018). One study estimates that two-thirds of patients rejected therapy with Optune® when recommended by their physician (Onken et al., 2018). Reasons that patients have reported rejecting using Optune® for GBM include not wanting to shave their head or wear a visible device, or incompatibility with continuing to work (50%). Other reasons included lack of social support to change the patches (17%) and technical challenges (8%). More recent estimates indicate that acceptance rates have increased over time to 68% as more physicians and patients have become aware of Optune® and the most recent effectiveness data (Onken et al., 2018).

Table 2. Incidence and 5-Year Survival Rates for GBM by Gender, Race, Age at Diagnosis and Location, United States

	Average Annual Adjusted Incidence Rates (per 100,000)	5-Year Survival Rates (Percent)
Overall	**3.21 (3.18-3.23)**	**5.6 (5.3-5.8)**
Male	4.00 (3.95-4.04)	5.4 (5.0-5.8)
Female	2.53 (2.50-2.56)	5.3 (4.9-5.8)
Age at Diagnosis		
0-19	0.18 (0.17-0.20)	16.6 (13.2-20.4)

	Average Annual Adjusted Incidence Rates (per 100,000)	5-Year Survival Rates (Percent)
20-34	0.46 (0.43-0.48)	19.1 (17.6-20.7)
35-44	1.25 (1.20-1.30)	*
45-54	3.55 (3.47-3.63)	7.7 (7.0-8.5)
55-64	8.05 (7.92-8.17)	4.7 (4.2-5.2)
65-74	12.99 (12.79-13.2)	2.6 (2.2-3.0)
75-84	15.13 (14.84-15.43)	1.0 (0.7-1.3)
85+	9.07 (8.73-9.42)	*
Race		
White	3.47 (3.44-3.50)	5.1 (4.8-5.4)
Black	1.80 (1.73-1.86)	7.2 (5.8-8.7)
American Indian/Alaskan Native	1.43 (1.24-1.65)	7.9 (3.6-14.5)
Asian/Pacific Islander	1.57 (1.48-1.66)	8.7 (6.9-10.7)
Hispanic	2.4 (2.32-2.47)	8.1 (7.0-9.4)
Location		
Urban	3.13 (3.10-3.16)	5.8 (5.5-6.1)
Rural	3.03 (2.97-3.10)	3.9 (3.2-4.6)

Source: Gittleman et al., 2018; Ostrom et al., 2018.

Notes: Other than the incidence rate and survival rates for those aged 0–19, the remainder of the data in this table reflect persons aged 20 and older.

*Five-year survival rates for ages 35–44 are presented in the cell above which represents data for ages 20–44; five-year survival rates for ages 85+ are included in the cell above which represents data for ages 75+.

Disparities[24] and Social Determinants of Health[25] in Cancer Treatment

Per statute, CHBRP includes discussion of disparities and social determinants of health (SDoH) as it relates to cancer treatment. Disparities are differences between groups that are modifiable. Although at this time, the only FDA-approved anticancer device, Optune®, is used to treat GBM, it is possible that in the future, there could be additional devices that would treat other forms of cancer. Therefore, since this

[24] Several competing definitions of "health disparities" exist. CHBRP relies on the following definition: Health disparity is defined as the differences, whether unjust or not, in health status or outcomes within a population. Wyatt et al., 2016.

[25] CHBRP defines social determinants of health as conditions in which people are born, grow, live, work, learn, and age. These social determinants of health (economic factors, social factors, education, physical environment) are shaped by the distribution of money, power, and resources and impacted by policy (adapted from Healthy People 2020, 2015; CDC, 2014). See CHBRP's SDoH white paper for further information: http://chbrp.com/analysis_methodology/public_health_impact_analysis.php.

mandate may have a wider impact in the future, a discussion of the disparities in relation to cancer overall is presented below.

The National Cancer Institute (NCI) notes that, across the United States, cancer disparities among racial/ethnic groups are closely associated with SDoH including income and built and social environments (e.g., stress, diet) (NCI, 2016). Numerous studies have documented that individuals from lower socioeconomic groups and specific racial and ethnic minorities have greater cancer risk and poorer cancer-related outcomes. This differential burden results in lower overall survival rates, a generally more advanced stage of cancer at time of diagnosis, and a higher eventual risk of death (Albain et al., 2009; Sloane, 2009). Compared with whites, African Americans have poorer survival once cancer is diagnosed. Five-year relative survival is lower in blacks than in whites within every stratum of stage of diagnosis for nearly every cancer site (Ward et al., 2004). As cancer treatments become more sophisticated, the disparity between whites and non-whites is likely to widen (Meropol and Schulman, 2007). This is likely because disparities in socioeconomic status lead to disparities in access to new medical advances and ultimately in health status. Therefore, medical advances (such as anticancer medical devices) may exacerbate disparities in relative racial/ethnic cancer survival rates (Tehranifar et al., 2009).

While ethnic minorities have higher rates of cancer overall and lower survival rates, a different pattern is seen when looking at GBM specifically. As presented in Table 2, analysis of the NCI Surveillance, Epidemiology, and End Results (SEER) database found that non-Hispanic whites have higher rates of incidence of GBM as well as lower 5-year survival rates compared to other racial/ethnic groups (Ostrom et al., 2018). In addition, a study using that same dataset adjusted for other factors such as age, gender, insurance status, location and size of the tumor, and type of surgery, and found that Asians and Pacific Islanders have better survival rates compared to non-Hispanic whites (Bohn et al., 2018). In terms of treatment for GBM, one study found that factors associated with not receiving therapy for GBM included being female, black, Hispanic, and of older age (Dressler et al., 2019).

MEDICAL EFFECTIVENESS

As noted in the *Background* section, the FDA has approved one anticancer medical device that CHBRP believes fits SB 746's definition of an anticancer medical device: Optune®. This device was first approved by the FDA in 2011 to treat patients with recurrent glioblastoma multiforme (GBM); further approval was granted in 2015 to treat patients newly diagnosed with GBM. Optune® delivers low-intensity tumor treating fields (TTFields) to the GBM tumor. TTFields are alternating electrical fields that pulse through the skin of the patient's scalp and disrupt the cancer cells' ability to divide and spread.

The medical effectiveness review summarizes findings from evidence[26] on the effectiveness of Optune® to treat GBM in adults, for which the device is FDA-approved. Although several preliminary studies are underway that assess the efficacy and safety of Optune® for pediatric GBM (Green et al., 2017), non-small cell lung cancer (Pless et al., 2013), pancreatic cancer (Rivera et al., 2019), and ovarian carcinoma (Vergote et al., 2018), CHBRP did not include these studies in its review because the FDA has not approved Optune® for treatment of these populations. Patients are currently being recruited into a pilot trial (Drexell Hunter Boggs) and a phase III randomized clinical trial (Novocure Ltd.) to study the effects of TTFields on brain metastases from lung cancer. Descriptions of both of these studies can be found at ClinicalTrials.gov. They are not included in CHBRP's analysis because no findings have been published to date.

Research Approach and Methods

Studies of Optune® were identified through searches of PubMed, the Cochrane Library, Web of Science, Embase, and Scopus. The search was limited to abstracts of studies published in English from 2010 to present because Optune® did not receive FDA approval until 2011.

The literature review returned abstracts for 288 articles, of which nine studies met the inclusion criteria in the medical effectiveness review. Articles were excluded for several reasons, with the most common ones being that the studies did not report findings from a research study, they did not address the effectiveness of Optune®, they illustrated the mechanism of action of TTFields (i.e., did not address efficacy of TTFields), or they were performed using computer-generated models.

The conclusions below are based on the best available evidence from published peer-reviewed and grey literature.

Key Questions

1. What is the impact of Optune® on health outcomes (e.g., mortality, remission, quality of life)?

2. Does the rate of compliance with Optune® (i.e., percent of hours in the day during which a person wears Optune®) affect the device's effectiveness?

3. Are there harms associated with using Optune®?

[26] Much of the discussion below is focused on reviews of available literature. However, as noted on page 11 of the Medical Effectiveness analysis and research approach document (posted here), in the absence of "fully-applicable to the analysis" peer-reviewed literature on well-designed randomized controlled trials (RCTs), CHBRP's hierarchy of evidence allows for the inclusion of other evidence.

Methodological Considerations

Nine articles were determined to be relevant to SB 746. Two articles — Stupp et al., 2017 (EF-14 trial); and Stupp et al., 2012 (EF-11 trial) — presented findings from the foundational randomized controlled trials (RCTs) that analyzed the effectiveness of Optune® on GBM. Both of these RCTs were funded by Novocure Ltd., the manufacturer of Optune®. Six studies (Kanner et al., 2014; Kesari and Ram 2017; Stupp et al., 2015; Taphoorn et al., 2018; Toms et al., 2019; and Zhu et al., 2017) were either interim or post-hoc analyses of the two foundational studies. One study analyzed data from a patient registry of people with recurrent GBM who received Optune® outside of a clinical trial (Mrugala et al., 2014). Table 3 summarizes key attributes of these studies, including what foundational RCT the analysis is based on and how the study outcome(s) differed.

Table 3. Key Attributes of Studies Included in the Medical Effectiveness Review

Study	Study Participants	Study Design	Study Outcome(s)
Stupp et al., 2012 (EF-11 RCT)	237 patients 18+ years old with histologically confirmed recurrent GBM who had completed radiotherapy with and without concomitant and/or adjuvant temozolomide (TMZ)	RCT with 1:1 randomization to TTFields alone (n=120) or active chemotherapy (n=117). Study was conducted at 28 institutions	Primary: overall survival Secondary: progression-free survival, quality of life, and safety
Kanner et al., 2014	See EF-11 RCT	Post-hoc analysis of EF-11 RCT data. Instead of analyzing the intent-to-treat (ITT) population, analyzed the “as treated” groups	Overall survival in subgroups of patients
Stupp et al., 2017 (EF-14 RCT)	695 patients 18+ years old with newly diagnosed GBM who had completed standard radiotherapy with concomitant TMZ	RCT with 2:1 randomization to TTFields+TMZ (n=466) or TMZ alone (n=229). Study was conducted at 83 centers	Primary: progression-free survival Secondary: overall survival, adverse events
Stupp et al., 2015	See EF-14 RCT	Interim analysis of EF-14 RCT conducted on the first 315 patients after at least 18 months of follow-up	Primary: progression-free survival Secondary: overall survival
Kesari and Ram, 2017	See EF-14 RCT	Post-hoc analysis of EF-14 RCT	Overall survival rates from day of first progression until death or censored event
Taphoorn et al., 2018	See EF-14 RCT	Secondary analysis of data from the EF-14 RCT	Quality of life, deterioration-free survival, and time to deterioration
Toms et al., 2019	See EF-14 RCT	Sub-group analysis of data from the EF-14 RCT. Correlated TTFields	Progression-free survival and overall survival given

Study	Study Participants	Study Design	Study Outcome(s)
		compliance with progression-free survival and overall survival vs. TMZ alone	the percentage of monthly treatment compliance
Zhu et al., 2017	See EF-14 RCT	Interim analysis of EF-14 RCT conducted on the first 315 patients after at least 18 months of follow-up	Quality of life at 3, 6, and 9 months out from baseline; cognitive status; functional status
Mrugala et al., 2014	Patient Registry Dataset (PRiDe) of recurrent GBM patients who received Optune® in a clinical practice setting	Outcomes of patients in PRiDe were compared to outcomes of patients in both groups of the EF-11 RCT using Kaplan-Meier curve estimates	Primary: overall survival Secondary: adverse events

Source: Kanner et al., 2014; Kesari and Ram, 2017; Mrugala et al., 2014; Stupp et al., 2012; Stupp et al., 2015; Stupp et al., 2017; Taphoorn et al., 2018; Toms et al., 2019; Zhu et al., 2017

Key: GBM = glioblastoma multiforme; PRiDe = Patient Registry Dataset; RCT = randomized controlled trial; TTFields = tumor treating fields; TMZ = temozolomide

Although both foundational studies were RCTs, they have some limitations. The design of the RCTs was such that patients in the intervention group received Optune® alone or plus chemotherapy, and patients in the control group received chemotherapy. This design did not blind participants to the type of treatment they received, which may bias the estimate of the size of the effect of Optune®. The research design would have been stronger if patients in the control group were fitted with a sham TTFields device, because this would have enabled the researchers to estimate the placebo effect associated with the device.

Outcomes Assessed

The nine articles included in CHBRP's review assessed the following outcomes: (1) overall survival; (2) progression-free survival; (3) quality of life and functional status; and (4) harms from the treatment.

Study Findings[27]

CHBRP found a preponderance of evidence that persons receiving Optune® have increased overall survival (i.e., the length of time during which the GBM does not get worse) compared to persons who receive standard care (e.g., active chemotherapy such as TMZ). There is limited evidence that Optune® increases progression-free survival among people with newly diagnosed GBM. Findings regarding improvements in functional status and quality of life measurements are inconclusive. There is limited evidence that using Optune® does not lead to more frequent or severe harms than standard of care.

[27] The figures in this section summarize CHBRP's findings regarding the strength of the evidence for the effects of Optune® on GBM addressed by SB 746. For test, treatments, and services for which CHBRP concludes that there is clear and convincing, preponderance, limited, or inconclusive evidence, the placement of the highlighted box indicates the strength of the evidence. If CHBRP concludes that evidence is insufficient, a figure that states "Insufficient Evidence" will be presented.

Overall Survival

Seven articles presented findings from the EF-11 and EF-14 RCTs regarding the impact of Optune® on overall survival for patients with GBM. The first article published regarding findings from EF-11 RCT examined an intent to treat (ITT) population (i.e., all randomized patients regardless of whether or not they received the treatment) of patients with recurrent GBM. Stupp et al. (2012) found no statistically significant improvement in the median length of overall survival among those in the intervention group versus those in the control group (active chemotherapy according to the physician's best choice). Persons in the intervention and control groups had median overall survival of 6.6 months and 6.0 months, respectively. A post-hoc analysis of this study that focused on the "as treated" population, which excluded 27 individuals because they did not receive at least one course of Optune®, found that the median overall survival for patients receiving at least one course of Optune® was significantly longer than for those who received chemotherapy (7.7 vs. 5.9 months) (Kanner et al., 2014). Another study that compared data from the Patient Registry Dataset (PRiDe), a database that captures "real-world" clinical use of Optune®, to the EF-11 RCT results found that overall survival rates for Optune® using real-world data were significantly longer than the rates found in the RCT (Mrugala et al., 2014). The median length of overall survival for patients using Optune® outside of the RCT was 9.6 months. However, this estimate of median overall survival from this observational study may be biased upward because patients who are followed more closely and receive better care to treat a recurrence of GBM may be more likely to be offered Optune® than other people with GBM who receive care outside of clinical trials. In addition, the percent of patients enrolled in the PRiDe study who were treated for a first recurrence of GBM was larger than the percent of patients in the EF-11 RCT who were treated for a first recurrence (Mrugala et al., 2014). This finding suggests that the impact of Optune® on overall survival may be greater among persons treated for a first recurrence of GBM than for subsequent recurrences.

The EF-14 RCT (Stupp et al., 2017) studied overall survival for patients newly diagnosed with GBM randomized to receive Optune® plus TMZ versus participants receiving TMZ alone. Those in the ITT population who received Optune® had longer median overall survival than those who did not (20.9 months versus 16.0 months). Stupp et al. (2015) found a similar result in their interim analysis of the same RCT. For the "as treated" population, the interim analysis found that those treated with Optune® in addition to TMZ had a median length of overall survival of 20.5 months versus 15.6 months among those who received TMZ alone. In the ITT population, the median overall survival was 19.6 months in the Optune® plus TMZ group and 16.6 months in the TMZ alone group. Kesari and Ram (2017) and Toms et al. (2019) also conducted analyses on the effect of Optune® on overall survival among patients enrolled in this RCT. Kesari and Ram (2017) performed a post-hoc analysis of the overall length of survival for RCT participants from the day of first progression. Patients treated with Optune® in addition to TMZ versus TMZ alone lived statistically significantly longer following the first day of progression — 11.8 months versus 9.2 months.

Toms et al. (2019), Kanner et al. (2014), and Mrugala et al. (2014) found that median overall survival was longer among patient subgroups who demonstrated greater compliance with their Optune® treatment regimen. Toms et al. (2019) looked at EF-14 RCT participants whose treatment compliance rate was at least 50% (i.e., the participant used Optune® at least 12 hours per day); they concluded that those participants in the Optune® plus TMZ group had a longer median overall length of survival than the TMZ only group with maximal survival benefit in the >90% compliance group. The median overall length of survival in the Optune® plus TMZ group with >90% compliance was 24.9 months compared to 16.0 months in the TMZ alone group with >90% compliance. Kanner et al. (2014) found that the median overall length of survival was significantly longer in patients receiving Optune® with a maximal monthly compliance rate of greater than or equal to 75% (i.e., used Optune® for at least 18 hours daily) versus those with a less than 75% compliance rate (7.7 months vs. 4.5 months, p=0.042). The study also showed a significant trend for improved median overall survival with higher compliance (p=0.039).

Mrugala et al. (2014) found a significant difference in median overall survival in patients with a daily compliance rate of greater than or equal to 75% versus those with a less than 75% compliance rate (13.5 months vs. 4.0 months, p<0.0001).

Toms et al. (2019) reported that 86% of the patients in the Optune® plus TMZ group had a compliance rate of at least 50% (n=388), and 10% of the patients had a compliance rate of at least 90% (n=10). In Kanner et al. (2014), 77% of the patients (n=92) in the Optune® group complied with the treatment at least 75% of the time. In Mrugala et al. (2014), 44% (n=127) of the patients achieved daily compliance of greater than or equal to 75%.

Summary of findings regarding effects on overall survival: There is a *preponderance of evidence* from two primary RCTs, one interim analysis, and four post-hoc analyses from these RCTs that Optune® increases median overall survival among adults with GBM.

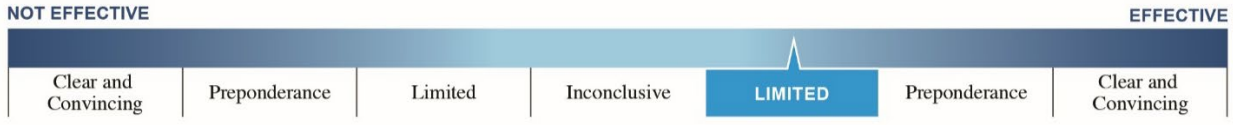
Figure 2. Effect of Optune® on Median Overall Survival Among Adults with GBM

Progression-Free Survival

Four studies examined whether the length of progression-free survival differed between intervention and control groups. Progression-free survival measures the length of time during which the GBM does not get worse. In the EF-11 RCT (Stupp et al., 2012), which analyzed outcomes for an ITT population with recurrent GBM, the difference in the progression-free survival rate at 6 months between the groups who received Optune® (intervention) and active chemotherapy (control) was not statistically significant (21.4% [intervention] and 15.1% [control], p=0.13). The EF-14 RCT (Stupp et al., 2017) found that median progression-free survival differed between people with newly diagnosed GBM who received Optune® and TMZ versus TMZ alone (6.7 months among patients receiving Optune® and TMZ and 4.0 months among patients receiving TMZ alone, respectively, p<0.001). Similar results were shown in the trial's interim analysis (Stupp et al., 2015), which looked at progression-free survival in the ITT population. Median progression-free survival was 7.1 months in the intervention group and 4.0 months in the control group. Toms et al. (2019) looked at EF-14 RCT participants whose treatment compliance rate was at least 50%; they concluded that those participants in the Optune® plus TMZ group had longer median progression-free survival than the TMZ only group, with maximal survival benefit in the >90% compliance group. Median progression-free survival in the Optune® plus TMZ group with >90% compliance was 8.2 months compared to 4.0 months in the TMZ alone group with >90% compliance.

Summary of findings regarding effects on progression-free survival: There is *limited evidence* from two primary RCTs, one interim analysis, and one post-hoc analysis from these RCTs that Optune® increases median progression-free survival among adults with newly diagnosed GBM.

Figure 3. Effect of Optune® on Median Progression-Free Survival Among Adults with Newly Diagnosed GBM



Quality of Life and Functional Status

Three studies examined the impact of Optune® on quality of life and functional status measures. The EF-11 RCT concluded that participants receiving Optune® had higher cognitive, emotional, and role functioning than participants receiving chemotherapy. However, the groups showed no numerical differences in global health (i.e., a composite quality of life measure) and social functioning, and the authors concluded that physical functioning "may be slightly worse" among Optune® users than chemotherapy users. None of the functional status measures assessed by this RCT were tested statistically; instead, the authors drew conclusions based on examining the prevalence rates between the two groups (Stupp et al., 2012).

The interim analysis of the EF-14 RCT (Zhu et al., 2017) showed no preliminary evidence that quality of life, cognitive status, and functional status were adversely affected by the continuous use of Optune®. Results from a secondary analysis of the same RCT (Taphoorn et al., 2018) concluded that quality of life measures did not differ significantly between the groups. Deterioration-free survival — defined as the time to a greater than 10-point deterioration in health-related quality of life scores from baseline without a subsequent 10-point improvement in scores, progressive disease, or death — was longer in the Optune® group for global health status, physical functioning, emotional functioning, pain, and leg weakness (all p-values <0.01).

Summary of findings regarding effects of Optune® use on quality of life and functional status measures: There is *inconclusive evidence* from one primary RCT, one interim analysis of an RCT, and one secondary analysis of an RCT regarding whether Optune® improves quality of life and functional status measures compared to usual care for GBM.

Figure 4. Effect of Optune® on Quality of Life and Functional Status

Harms

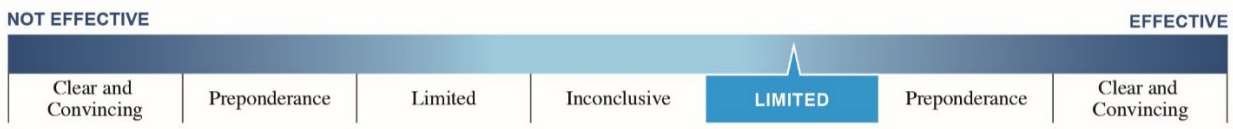
Four studies formally assessed harms associated with Optune®: the EF-11 RCT; the PRiDe analysis, which compared outcomes of patients in a "real world" setting to those in both the intervention and comparison groups in the EF-11 RCT; the EF-14 RCT; and the secondary analysis of the EF-14 RCT done by Taphoorn et al. (2018). Additional articles discussed harms, but they either did not designate them as primary or secondary endpoints (i.e., the studies were not appropriately powered to test for differences in harms between groups) or did not provide the results of statistical tests of the significance

of differences between the intervention and comparison groups. Because of this, these studies were excluded in CHBRP's analysis on harms.

The EF-11 RCT (Stupp et al., 2012) found that 6% of the patients treated with Optune® experienced a severe adverse event, compared to 16% of those treated with chemotherapy (p=0.022). The PRiDe analysis (Mrugala et al., 2014) found that "No new adverse events were detected in PRiDe compared to those found in EF-11." Contact dermatitis was the most common harm found in the EF-11 RCT (16.0% of the patients treated with Optune®), and "skin reaction" was the most common harm found in the PRiDe analysis (24.3% of the patients treated with Optune® in PRiDe). These harms were caused by the device's transducer patches. Although the EF-14 RCT (Stupp et al., 2017) found that mild to moderate skin toxicity existed underneath the transducer patches in 52% of the patients who received Optune®, the researchers did not find a statistically significant difference in the overall incidence, distribution, or severity of adverse events between the intervention and control groups. The analysis done by Taphoorn et al. (2018) found that more people in the Optune® plus TMZ group reported "itchy skin" as a side effect compared to those in the TMZ alone group; this side effect was significantly worse at 3, 6, and 9 months of treatment, but not at 12 months.

Summary of findings regarding harms associated with Optune® use: There is *limited evidence* from two primary RCTs and two secondary analyses that using Optune® is associated with skin irritation but is not associated with more frequent or severe harms than usual care for GBM.

Figure 5. Harms of Optune®



BENEFIT COVERAGE, UTILIZATION, AND COST IMPACTS

As discussed in the *Policy Context* section, SB 746 would require DMHC-regulated health plans and CDI-regulated policies that cover chemotherapy or radiation therapy for the treatment of cancer to also cover FDA-approved anticancer medical devices that are to be used outside of a medical facility.

This section reports the potential incremental impacts of SB 746 on estimated baseline benefit coverage, utilization, and overall cost. As mentioned in the *Policy Context* section, CHBRP found only one such device, Optune®, which is used for the treatment of glioblastoma multiforme (GBM), a type of brain cancer, that is currently approved by the FDA (as of March 2019).[28] It is possible that other devices will become available in the future, or that Optune® will be approved for the treatment of other types of cancer. For this analysis, CHBRP focused on the use of Optune® to treat GBM because it is the only anticancer device on the market today that meets the specifications of SB 746. According to the bill, "anticancer medical device" means a medical device, including component parts, services, and supplies necessary for the effective use of the device.

Key Assumptions

- SB 746 would not impact any form of cost sharing, such as deductibles, copayments, and coinsurance.
- SB 746 would not affect plan or insurer use of utilization management, such as prior authorization requirements and review for medical necessity.

For further details on the underlying data sources and methods used in this analysis, please see Appendix C.

Baseline and Postmandate Benefit Coverage

Currently, among enrollees with health insurance that would be subject to SB 746, 91% have coverage for Optune®. Current coverage of Optune® was determined by a survey of the largest (by enrollment) providers of health insurance in California. Responses to this survey represent 82% of enrollees with private market health insurance that can be subject to state mandates. All health plans and policies that cover Optune® do so under the durable medical equipment (DME) benefit, and any cost-sharing requirements for DME, such as deductibles, copayments, and coinsurance, apply to Optune®. Some insurers also require review for medical necessity or prior authorization. One plan indicated that its coverage was for newly diagnosed cases of GBM only and that other uses were considered investigational. CHBRP assumes that these benefit designs would not change under SB 746 and that those plans and insurers without coverage would need to provide coverage postmandate (see estimates in Table 1). CHBRP confirmed similar impacts on other market segments such as CalPERS and several of the larger (by enrollment) Medi-Cal MCPs. CHBRP assumes that all health plans and policies will be in compliance with the proposed mandate.

Baseline and Postmandate Utilization

CHBRP is not able to quantify the baseline utilization data due to limitations in health insurance claims data. CHBRP estimated the baseline and postmandate utilization based on the existing literature and

[28] Personal communication with Jonathan S. Helfgott, March 2019.

content experts' input instead. As mentioned in the *Background* section, it is estimated that there will be 1,200 (3.21 cases per 100,000 people) new cases of GBM in California each year, mostly among adults aged 65 and above (ACS, 2019; Ostrom et al., 2018). SB 746 would not affect coverage for most older adults with GBM because most have coverage through the Medicare program, which is not subject to state benefit mandates. Based on a published study (Onken et al., 2018, 30% of patients with a primary diagnosis of GBM were informed about TTFields (Optune®). Among patients informed about Optune®, the acceptance rate was 36% (Onken et al., 2018). Based on the age-adjusted incidence rate, CHBRP estimated that there will be 56 adult enrollees with coverage subject to SB 746 using Optune® in the baseline year. Even with insurance coverage for Optune®, patients may decide not to use it due to factors including necessity of head shaving, frequent patch change every 3–4 days, weight of the device and need for spare batteries, visibility of the patches, increased sweating in warm air temperatures, and mobility issues while carrying the device (Onken et al., 2018; Topfer and Farrah, 2018). Patients who live longer due to the use of Optune® may incur use of other services (e.g., chemotherapy), but CHBRP did not include those in the utilization and cost impact estimates due to limitations of current claims data. Only 29 unique users were identified in Milliman's 2016 Consolidated Health Cost Guidelines™ Sources Database (CHSD) and the 2016 MarketScan® Commercial Claims and Encounters Databases; the sample sizes are too small to develop a reliable estimate.

Postmandate, based on CHBRP expert opinion, it is estimated that the utilization of Optune® may increase 10% due to increased awareness and acceptance of the treatment by both providers and patients, which would result in five more users. Physicians who currently prescribe Optune® must receive training and certification to do this, although the process is very manageable (Topfer and Farrah, 2018). See estimates in Table 1.

Baseline and Postmandate Per-Unit Cost

The cost of Optune® is $21,000 per user per month, which includes component parts, services, and supplies necessary for the effective use of the device (Topfer and Farrah, 2018). Based on Milliman's 2016 CHSD and the 2016 MarketScan® Commercial Claims and Encounters Databases, the average cost paid by health plans and insurers is $18,624 per month per user. The average length of Optune® use is 5.2 months per user (Topfer and Farrah, 2018). CHBRP estimates the average cost will be $96,845 per user. Since the expected utilization increase is minimal and Optune® unit cost has remained constant since it came to the market, CHBRP assumes SB 746 would have no impact on per-unit cost postmandate. See estimates in Table 1.

Baseline and Postmandate Expenditures

Table 4 and Table 5 present baseline and postmandate expenditures by market segment for DMHC-regulated plans and CDI-regulated policies. The tables present per member per month (PMPM) premiums, enrollee expenses for both covered and noncovered benefits, and total expenditures (premiums as well as enrollee expenses).

SB 746 would increase total net annual expenditures by $648,000 or 0.0004% for enrollees with DMHC-regulated plans and CDI-regulated policies. This is due to a $717,000 increase in total health insurance premiums paid by employers and enrollees for newly covered benefits, adjusted by an increase in enrollee expenses for covered and/or noncovered benefits.

Premiums

Changes in premiums as a result of SB 746 would vary by market segment. Note that such changes are related to the number of enrollees (see Table 1, Table 4, and Table 5) with health insurance that would be subject to SB 746.

The mandate is estimated to increase premiums by about $717,000. The distribution of the impact on premiums is as follows:

- Total premiums for private employers purchasing group health insurance are estimated to increase by $377,000 or 0.0004%.
- Total employer premium expenditures for CalPERS HMOs are estimated to increase by $11,000, or 0.0004%.

Of the amount CalPERS would pay in additional total premiums, about $9,000 would be the cost borne by the General Fund for CalPERS HMO members who are state employees or their dependents.

- Enrollee contributions toward premiums for group insurance are estimated to increase by $78,000, or 0.0005%.
- Total premiums for purchasers of individual market health insurance are estimated to increase by $73,000, or 0.0006%.

The premium changes among privately funded market segments are less than $0.01 PMPM. Among publicly funded DMHC-regulated health plans, the impacts for DMHC-regulated enrollees associated with Medi-Cal MCPs and with CalPERS are also very similar, less than $0.01 PMPM.

CHBRP estimates there will be a $177,000 increase in expenditures for the 7.6 million Medi-Cal beneficiaries enrolled in DMHC-regulated plans.

Enrollee Expenses

SB 746–related changes in enrollee expenses for covered benefits (e.g., deductibles, copayments) and enrollee expenses for noncovered benefits would vary by market segment. Note that such changes are related to the number of enrollees (see Table 1,Table 4, and Table 5) with health insurance that would be subject to SB 746 and expected to use Optune® during the year after enactment.

CHBRP projects no change to copayments or coinsurance for those with coverage but does project an increase in utilization of Optune® and therefore an increase in overall enrollee cost sharing. However, health plans that do not currently cover Optune® can set cost-sharing requirements once coverage is mandated (e.g., they may require higher cost-sharing amounts).

It is possible that some enrollees premandate have incurred expenses related to use of Optune® for which coverage was denied, but CHBRP cannot estimate the frequency with which such situations occur and so cannot offer a calculation of impact. In some of these cases, it is possible the device would be provided through the manufacturer's patient assistance program.

Potential Cost Offsets or Savings in the First 12 Months After Enactment

CHBRP does not project any cost offsets or savings in health care that would result because of the enactment of provisions in SB 746 since Optune® is used to complement other standard treatments.

Patients who live longer due to the use of Optune® may incur additional medical treatment costs (Bernard-Arnoux et al., 2016), but CHBRP did not include those in the cost impact estimates due to limitations of the claims data mentioned above. French researchers examined the cost effectiveness of Optune®; they found that adding TTFields therapy to standard of care resulted in increases of life expectancy of 4.08 months (0.34 Life Year Gained [LYG]) and cost (in euros) of €185,476 per patient (Bernard-Arnoux et al., 2016), with the Incremental Cost Effectiveness Ratio (ICER) of €549,909/LYG. The most influential factor on the ICER was the cost of TTFields therapy (€21,000 per month), followed equally by additional monthly treatment costs (€1,532 to €3,572) for both prolonged overall survival and progression-free survival periods. The probabilistic sensitivity analysis showed a 95% confidence interval of the ICER of €447,017/LYG to €745,805/LYG with 0% chance to be cost-effective.

Postmandate Administrative Expenses and Other Expenses

CHBRP estimates that the increase in administrative costs of DMHC-regulated plans and CDI-regulated policies will remain proportional to the increase in premiums. CHBRP assumes that if health care costs increase as a result of increased utilization or changes in unit costs, there is a corresponding proportional increase in administrative costs. CHBRP assumes that the administrative cost portion of premiums is unchanged. All health plans and insurers include a component for administration and profit in their premiums.

Other Considerations for Policymakers

In addition to the impacts a bill may have on benefit coverage, utilization, and cost, related considerations for policymakers are discussed below.

Postmandate Changes in the Number of Uninsured Persons[29]

Because the change in average premiums does not exceed 1% for any market segment (see Table 1, Table 4, and Table 5), CHBRP would expect no measurable change in the number of uninsured persons due to the enactment of SB 746.

Changes in Public Program Enrollment

CHBRP estimates that the mandate would produce no measurable impact on enrollment in publicly funded insurance programs due to the enactment of SB 746.

How Lack of Benefit Coverage Results in Cost Shifts to Other Payers

In general, CHBRP assumes that in some cases, patients' use of Optune® will not be covered by their health plan or policy (i.e., coverage will be denied because the device was not deemed to be medically necessary). However, no cost shift to other payers is expected due to the existence of the manufacturer's patient assistance program.

[29] See also CHBRP's *Uninsured: Criteria and Methods for Estimating the Impact of Mandates on the Number of Individuals Who Become Uninsured in Response to Premium Increases (December 2015)*, available at http://chbrp.com/analysis_methodology/cost_impact_analysis.php.

Table 4. Baseline Per Member Per Month Premiums and Total Expenditures by Market Segment, California, 2020

	DMHC-Regulated						CDI-Regulated			
	Privately Funded Plans (by Market) (a)			Publicly Funded Plans			Privately Funded Plans (by Market) (a)			
	Large Group	*Small Group*	*Individual*	*CalPERS HMOs (b)*	*MCMC (Under 65) (c)*	*MCMC (65+) (c)*	*Large Group*	*Small Group*	*Individual*	**Total**
Enrollee counts										
Total enrollees in plans/policies subject to state mandates (d)	10,565,000	3,099,000	2,184,000	523,000	6,796,000	795,000	318,000	108,000	102,000	24,490,000
Total enrollees in plans/policies subject to SB 746	10,565,000	3,099,000	2,184,000	523,000	6,796,000	795,000	318,000	108,000	102,000	24,490,000
Premiums										
Average portion of premium paid by employer	$555.35	$341.99	$0.00	$493.71	$268.13	$694.55	$710.92	$462.84	$0.00	$118,029,198,000
Average portion of premium paid by employee	$39.66	$205.44	$437.39	$94.04	$0.00	$0.00	$250.37	$202.64	$475.67	$26,521,718,000
Total premium	**$595.01**	**$547.43**	**$437.39**	**$587.76**	**$268.13**	**$694.55**	**$961.29**	**$665.48**	**$475.67**	$144,550,916,000
Enrollee expenses										
For covered benefits (deductibles, copays, etc.)	$46.18	$121.03	$115.38	$48.33	$0.00	$0.00	$162.44	$186.84	$168.51	$14,750,880,000
For noncovered benefits (e)	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0
Total expenditures	**$641.19**	**$668.46**	**$552.77**	**$636.08**	**$268.13**	**$694.55**	**$1,123.73**	**$852.31**	**$644.18**	$159,301,796,000

Source: California Health Benefits Review Program, 2019.

Notes: (a) Includes enrollees with grandfathered and nongrandfathered health insurance acquired outside or through Covered California (the state's health insurance marketplace).

(b) Approximately 56.17% of CalPERS enrollees in DMHC-regulated plans are state retirees, state employees, or their dependents. About one in five (20.5%) of these enrollees has a pharmacy benefit not subject to DMHC.[30] CHBRP has projected no impact for those enrollees. However, CalPERS could, postmandate, require equivalent coverage for all its members (which could increase the total impact on CalPERS).

(c) Medi-Cal Managed Care Plan expenditures for members over 65 include those who are also Medicare beneficiaries. This population does not include enrollees in COHS.

(d) Enrollees in plans and policies regulated by DMHC or CDI aged 0 to 64 years as well as enrollees 65 years or older in employer-sponsored health insurance. This group includes commercial enrollees (including those associated with Covered California or CalPERS) and Medi-Cal beneficiaries enrolled in DMHC-regulated plans.[31]

(e) Includes only those expenses that are paid directly by enrollees or other sources to providers for services related to the mandated benefit that are not currently covered by insurance. This only includes those expenses that would be newly covered, postmandate. Other components of expenditures in this table include all health care services covered by insurance.

Key: CalPERS HMOs = California Public Employees' Retirement System Health Maintenance Organizations; CDI = California Department of Insurance; COHS = County Organized Health Systems; DMHC = Department of Managed Health Care; MCMC = Medi-Cal Managed Care.

[30] For more detail, see *Estimates of Pharmacy Benefit Coverage*, available at http://chbrp.com/analysis_methodology/cost_impact_analysis.php).
[31] For more detail, see *Estimates of Sources of Health Insurance in California*, available at http://chbrp.com/analysis_methodology/cost_impact_analysis.php.

Table 5. Postmandate Per Member Per Month Premiums and Total Expenditures by Market Segment, California, 2020

	DMHC-Regulated						CDI-Regulated			
	Privately Funded Plans (by Market) (a)			Publicly Funded Plans			Privately Funded Plans (by Market) (a)			
	Large Group	*Small Group*	*Individual*	*CalPERS HMOs (b)*	*MCMC (Under 65) (c)*	*MCMC (65+) (c)*	*Large Group*	*Small Group*	*Individual*	**Total**
Enrollee counts										
Total enrollees in plans/policies subject to state mandates (d)	10,565,000	3,099,000	2,184,000	523,000	6,796,000	795,000	318,000	108,000	102,000	24,490,000
Total enrollees in plans/policies subject to SB 746	10,565,000	3,099,000	2,184,000	523,000	6,796,000	795,000	318,000	108,000	102,000	24,490,000
Premiums										
Average portion of premium paid by employer	$0.0020	$0.0015	$0.0000	$0.0018	$0.0011	$0.0091	$0.0169	$0.0016	$0.0000	$566,000
Average portion of premium paid by employee	$0.0001	$0.0009	$0.0027	$0.0003	$0.0000	$0.0000	$0.0060	$0.0007	$0.0027	$152,000
Total premium	$0.0021	$0.0025	$0.0027	$0.0021	$0.0011	$0.0091	$0.0229	$0.0024	$0.0027	**$717,000**
Enrollee expenses										
For covered benefits (deductibles, copays, etc.)	$0.0000	-$0.0001	$0.0000	$0.0000	$0.0000	$0.0000	-$0.0176	$0.0000	$0.0000	-$68,000
For noncovered benefits (e)	$0.0000	$0.0000	$0.0000	$0.0000	$0.0000	$0.0000	$0.0000	$0.0000	$0.0000	$0
Total expenditures	$0.0021	$0.0024	$0.0027	$0.0021	$0.0011	$0.0091	$0.0053	$0.0024	$0.0027	**$649,000**
Percent change										
Premiums	0.0004%	0.0005%	0.0006%	0.0004%	0.0004%	0.0013%	0.0024%	0.0004%	0.0006%	0.0005%
Total expenditures	0.0003%	0.0004%	0.0005%	0.0003%	0.0004%	0.0013%	0.0005%	0.0003%	0.0004%	0.0004%

Source: California Health Benefits Review Program, 2019.

Notes: (a) Includes enrollees with grandfathered and nongrandfathered health insurance acquired outside or through Covered California (the state's health insurance marketplace).

(b) Approximately 56.17% of CalPERS enrollees in DMHC-regulated plans are state retirees, state employees, or their dependents. About one in five (20.5%) of these enrollees has a pharmacy benefit not subject to DMHC.[32] CHBRP has projected no impact for those enrollees. However, CalPERS could, postmandate, require equivalent coverage for all its members (which could increase the total impact on CalPERS).

(c) Medi-Cal Managed Care Plan expenditures for members over 65 include those who are also Medicare beneficiaries. This population does not include enrollees in COHS.

(d) Enrollees in plans and policies regulated by DMHC or CDI aged 0 to 64 years as well as enrollees 65 years or older in employer-sponsored health insurance. This group includes commercial enrollees (including those associated with Covered California or CalPERS) and Medi-Cal beneficiaries enrolled in DMHC-regulated plans.[33]

(e) Includes only those expenses that are paid directly by enrollees or other sources to providers for services related to the mandated benefit that are not currently covered by insurance. This only includes those expenses that would be newly covered, postmandate. Other components of expenditures in this table include all health care services covered by insurance.

Key: CalPERS HMOs = California Public Employees' Retirement System Health Maintenance Organizations; CDI = California Department of Insurance; COHS = County Organized Health Systems; DMHC = Department of Managed Health Care; MCMC = Medi-Cal Managed Care.

[32] For more detail, see *Estimates of Pharmacy Benefit Coverage*, available at http://chbrp.com/analysis_methodology/cost_impact_analysis.php).
[33] For more detail, see *Estimates of Sources of Health Insurance in California*, available at http://chbrp.com/analysis_methodology/cost_impact_analysis.php.

PUBLIC HEALTH IMPACTS

As discussed in the *Policy Context* section, SB 746 would require plans and policies that cover chemotherapy or radiation therapy for the treatment of cancer to also cover FDA-approved anticancer medical devices that are to be used outside of a medical facility. The public health impact analysis includes estimated impacts of SB 746 in the short term (within 12 months of implementation) and in the long term (beyond the first 12 months postmandate). This section estimates the short-term impact[34] of SB 746 on outcomes such as overall survival rate, progression-free survival rate, quality of life and functional status, and adverse events due to Optune®. See *Long-Term Impacts* for discussion of premature death, economic loss, and social determinants of health.

Estimated Public Health Outcomes

As presented in the *Medical Effectiveness* section, CHBRP found a preponderance of evidence that persons receiving Optune® have increased overall survival and limited evidence that Optune® increases progression-free survival among people with newly diagnosed GBM compared to persons who receive standard of care. Findings regarding improvements in functional status and quality of life measurements are inconclusive. There is limited evidence that using Optune® does not lead to more frequent or severe adverse events than standard of care.

As presented in the *Benefit Coverage, Utilization, and Cost Impacts* section, currently there is wide-spread insurance coverage for Optune®. It is anticipated that due to publicity around the passage of SB 746 there may be an increase in utilization of Optune® by 10%, leading to an additional five GBM patients utilizing Optune® as part of their GBM therapy. The research presented in the *Medical Effectiveness* section indicates that the median increase in survival time for those using Optune® is approximately 5 months.

Despite a preponderance of evidence that Optune® is medically effective, CHBRP projects no measurable public health impact at the population level due to the small estimated increase in utilization. However, SB 746 would likely yield increased length of life among the additional five enrollees who would use Optune® in the treatment of GBM.

Potential Harms From SB 746

When data are available, CHBRP estimates the marginal change in relevant harms associated with interventions affected by the proposed mandate. In the case of SB 746, as reported in the *Medical Effectiveness* section, there is no evidence to suggest that an increase in the use of Optune® could result in additional harm to enrollees with GBM.

Impact on Disparities[35]

As reported in the *Background* section, non-Hispanic whites have higher rates of incidence of GBM as well as lower 5-year survival rates compared to other racial/ethnic groups (Ostrom et al., 2018). In

[34] CHBRP defines short-term impacts as changes occurring within 12 months of bill implementation.
[35]. For details about CHBRP's methodological approach to analyzing disparities, see the *Benefit Mandate Structure and Unequal Racial/Ethnic Health Impacts* document here: http://chbrp.com/analysis_methodology/public_health_impact_analysis.php.

addition, in terms of treatment for GBM, one study found that factors associated with not receiving therapy for GBM including being female, black, Hispanic, and of older age (Dressler et al., 2019).

Racial or ethnic disparities in the prevalence and treatment of GBM exist; however, CHBRP did not find evidence to suggest that SB 746 would impact utilization of Optune® differentially by race or ethnicity. Despite an estimated increase in utilization of Optune®, CHBRP projects no impact on racial or ethnic disparities related to GBM treatment and survival.

LONG-TERM IMPACTS

In this section, CHBRP estimates the long-term impacts,[36] defined as those occurring beyond the first 12 months after implementation, of SB 746. These estimates are qualitative and based on the existing evidence available in the literature. CHBRP does not provide quantitative estimates of long-term impacts because of unknown improvements in clinical care, changes in prices, implementation of other complementary or conflicting policies, and other unexpected factors.

Long-Term Utilization and Cost Impacts

Utilization Impacts

After the estimated increase in utilization in the first 12 months, there is no indication in the research literature that the trend of utilization and incidence rate of enrollees with GBM will change over time. However, in the long term, it is possible that Optune® could be improved (e.g., become lighter) and have wider utilization as the treatment becomes more normalized and patient acceptance increases. In addition, as described in the *Medical Effectiveness* section, there are several preliminary studies underway that assess the efficacy and safety of Optune® for other conditions and populations such as pediatric GBM, non-small cell lung cancer, pancreatic cancer, ovarian cancer, and cancer that has metastasized in the brain from other locations. There may be more anticancer medical devices that come to the market in the future. If that happens, the overall utilization of anticancer devices will increase.

Cost Impacts

If the utilization of anticancer medical devices increases, CHBRP estimates that the cost will go up as well. As mentioned above, based on a cost-effectiveness study of Optune® conducted in France, the most influential factor on the Incremental Cost Effectiveness Ratio (ICER) for Optune® was the cost of the device (€21,000), followed equally by additional monthly treatment costs (€1,532 to €3,572) for both prolonged overall survival and progression-free survival periods.

Long-Term Public Health Impacts

Some interventions in proposed mandates provide immediate measurable impacts (e.g., maternity service coverage or acute care treatments) while other interventions may take years to make a measurable impact (e.g., coverage for tobacco cessation or vaccinations). When possible, CHBRP estimates the long-term effects (beyond 12 months postmandate) to the public's health that would be attributable to the mandate, including impacts on social determinants of health, premature death, and economic loss.

In the case of SB 746, CHBRP estimates that although there may not be any change in insurance coverage for Optune®, utilization of Optune® would increase 10% due to the publicity and increased awareness surrounding the passage of the legislation. As referenced above, Optune® could have wider utilization in the long term. CHBRP did not include these studies in its review as Optune® is not currently approved for treatment of other cancers. In addition, it is uncertain what impact Optune® could have on survival rates for these cancers, yet there is potential that it will extend survival time, as it does for GBM patients, but it is also possible that it will not be as effective with other types of cancers. Additionally, it is

[36] See also CHBRP's *Criteria and Guidelines for the Analysis of Long-Term Impacts on Healthcare Costs and Public Health*, available at http://www.chbrp.org/analysis_methodology/cost_impact_analysis.php.

unknown to what extent there will be other anticancer medical devices that are approved by the FDA in the future that will have the potential to significantly impact the public's health.

Therefore, the potential long-term impact of SB 746 is unknown, although it stands to reason that there is the potential for a larger impact in the long-term should Optune® be FDA-approved to treat other cancers and if the FDA approves other anticancer medical devices that are effective at treating cancer.

Impacts on Premature Death and Economic Loss

Premature death

Premature death is often defined as death occurring before the age of 75 years (Cox, 2006).[37] In California, it is estimated that there are nearly 102,000 premature deaths each year, accounting for about 1.9 million years of potential life lost (YPLL) (CDPH, 2009). Cancer represents the greatest contributor to premature death in California, with 21.1% of all YPLL attributable to cancer (CDPH, 2009). It is estimated that in California in 2007, the YPLL due to cancer was 1,209 per 100,000 population per year, corresponding to an annual state total of nearly 200,000 YPLL (CDPH, 2009). Although incidence rates of brain and other CNS tumors are low compared to other cancers, the mortality rates are much higher, especially for GBM (Rouse et al., 2016; Ostrom et al., 2018). In addition, the mean YPLL for brain and other CNS tumors are higher compared to other common cancers (Rouse et al., 2016).

Despite a preponderance of evidence that Optune® is medically effective, CHBRP projects no measurable impact in premature death at the population level due to the small estimated increase in utilization and survival time. However, SB 746 would likely yield an increase in survival time of 5 months for the additional five enrollees who would use Optune® in the treatment of GBM, leading to an overall increase in survival of 25 months. Future reductions in premature death may be even higher if Optune® is found to be effective in treating other types of cancers or if other anticancer medical devices are approved by the FDA.

Economic loss

Economic loss associated with disease is generally presented in the literature as an estimation of the value of the YPLL in dollar amounts (i.e., valuation of a population's lost years of work over a lifetime). In addition, morbidity associated with the disease or condition of interest can also result in lost productivity by causing a worker to miss days of work due to illness or acting as a caregiver for someone else who is ill.

SB 746 would likely yield an increase in survival time of 5 months for the additional five enrollees who would use Optune® in the treatment of GBM. As the majority of the population impacted by SB 746 are of working age, it is likely that this increase in survival time may lead to an increase in productivity and a decrease in economic loss associated with GBM. Similarly to reduction in premature death, in the long term, there is a possibility that SB 746 could have an even larger impact on a reduction in economic loss should Optune® be approved for other types of cancers or if other effective anticancer medical devices are approved by the FDA.

[37] The overall impact of premature death due to a particular disease can be measured in years of potential life lost prior to age 75 and summed for the population (generally referred to as "YPLL") (Cox, 2006). For more information about CHBRP's public health methodology, see http://chbrp.com/analysis_methodology/public_health_impact_analysis.php.

APPENDIX A TEXT OF BILL ANALYZED

On February 25, 2019, the California Senate Committee on Health requested that CHBRP analyze SB 746.

SENATE BILL **No. 746**

Introduced by Senator Bates
(Coauthor: Senator Wilk)

February 22, 2019

An act to add Section 1367.667 to the Health and Safety Code, and to add Section 10123.837 to the Insurance Code, relating to health care coverage.

LEGISLATIVE COUNSEL'S DIGEST

SB 746, as introduced, Bates. Health care coverage: anticancer medical devices.
Existing law, the Knox-Keene Health Care Service Plan Act of 1975, provides for the licensure and regulation of health care service plans by the Department of Managed Health Care, and makes a willful violation of the act a crime. Existing law requires health care service plan contracts and health insurance policies to cover certain medical services for particular types of cancer, including the screening, diagnosis, and treatment of breast cancer, and the screening and diagnosis of prostate cancer, if the contract or policy was issued, amended, or renewed after the applicable date.

This bill would require health care service plan contracts and health insurance policies issued, amended, or renewed on or after January 1, 2020, that cover chemotherapy or radiation therapy for the treatment of cancer to also cover anticancer medical devices. The bill would define "anticancer medical device" as a medical device that has been approved for marketing by the federal Food and Drug Administration or is exempt from that approval, is primarily designed to be used outside of a medical facility, and has been prescribed by an authorized provider upon the provider's determination that the device is medically reasonable and necessary for the treatment of the patient's cancer. Because a violation of this bill's provisions by a health care service plan would be a crime, the bill would impose a state-mandated local program.

The California Constitution requires the state to reimburse local agencies and school districts for certain costs mandated by the state. Statutory provisions establish procedures for making that reimbursement.

This bill would provide that no reimbursement is required by this act for a specified reason.

DIGEST KEY
Vote: majority Appropriation: no Fiscal Committee: yes Local Program: yes

---

BILL TEXT

THE PEOPLE OF THE STATE OF CALIFORNIA DO ENACT AS FOLLOWS:

SECTION 1.

Section 1367.667 is added to the Health and Safety Code, immediately following Section 1367.665, to read:

1367.667. (a) Every health care service plan contract issued, amended, or renewed in this state on or after January 1, 2020, that provides coverage for chemotherapy or radiation therapy for the treatment of cancer, shall also provide coverage for anticancer medical devices.

(b) For purposes of this section, "anticancer medical device" means a medical device, including component parts, services, and supplies necessary for the effective use of the device, that meets all of the following criteria:

(1) The device has been cleared or approved for marketing by the federal Food and Drug Administration, if that clearance or approval is required by law.

(2) The device is primarily and substantially designed for use outside of a medical treatment facility, or use for which reimbursement is not ordinarily provided as incident to a provider's professional service or as part of a provider's fee for service.

(3) The device is prescribed by a provider authorized to prescribe that device for the treatment of cancer, upon a determination by the provider that the device is medically reasonable and necessary for the treatment of the patient.

SEC. 2.

Section 10123.837 is added to the Insurance Code, immediately following Section 10123.835, to read:

10123.837. (a) Every policy of disability insurance that covers hospital, medical, or surgical expenses that is issued, amended, or renewed in this state on or after January 1, 2020, and provides coverage for chemotherapy or radiation therapy for the treatment of cancer, shall also provide coverage for anticancer medical devices.

(b) For purposes of this section, “anticancer medical device” means a medical device, including component parts, services, and supplies necessary for the effective use of the device, that meets all of the following criteria:

(1) The device has been cleared or approved for marketing by the federal Food and Drug Administration, if that clearance or approval is required by law.

(2) The device is primarily and substantially designed for use outside of a medical treatment facility, or use for which reimbursement is not ordinarily provided as incident to a provider’s professional service or as part of a provider’s fee for service.

(3) The device is prescribed by a provider authorized to prescribe that device for the treatment of cancer, upon a determination by the provider that the device is medically reasonable and necessary for the treatment of the patient.

SEC. 3.

No reimbursement is required by this act pursuant to Section 6 of Article XIII B of the California Constitution because the only costs that may be incurred by a local agency or school district will be incurred because this act creates a new crime or infraction, eliminates a crime or infraction, or changes the penalty for a crime or infraction, within the meaning of Section 17556 of the Government Code, or changes the definition of a crime within the meaning of Section 6 of Article XIII B of the California Constitution.

APPENDIX B LITERATURE REVIEW METHODS

This appendix describes methods used in the medical effectiveness literature review conducted for this report. A discussion of CHBRP's system for grading evidence, as well as lists of MeSH Terms, publication types, and keywords, follows.

Studies of the effects of Studies of Optune® were identified through searches of PubMed, the Cochrane Library, Web of Science, Embase, and Scopus.

The search was limited to abstracts of studies published in English. The medical effectiveness search was limited to studies published from 2010 to present because Optune® did not receive FDA approval until 2011. As discussed previously, SB 746 would only require coverage for anticancer medical devices approved by the FDA.

Reviewers screened the title and abstract of each citation retrieved by the literature search to determine eligibility for inclusion. The reviewers acquired the full text of articles that were deemed eligible for inclusion in the review and reapplied the initial eligibility criteria.

The literature review returned abstracts for 288 articles, of which 17 were reviewed for inclusion in this report. A total of nine articles were included in the medical effectiveness review for SB 746.

Evidence Grading System

In making a "call" for each outcome measure, the medical effectiveness lead and the content expert consider the number of studies as well the strength of the evidence. Further information about the criteria CHBRP uses to evaluate evidence of medical effectiveness can be found in CHBRP's *Medical Effectiveness Analysis Research Approach.*[38] To grade the evidence for each outcome measured, the team uses a grading system that has the following categories:

- Research design;
- Statistical significance;
- Direction of effect;
- Size of effect; and
- Generalizability of findings.

The grading system also contains an overall conclusion that encompasses findings in these five domains. The conclusion is a statement that captures the strength and consistency of the evidence of an intervention's effect on an outcome. The following terms are used to characterize the body of evidence regarding an outcome:

- Clear and convincing evidence;
- Preponderance of evidence;
- Limited evidence;
- Inconclusive evidence; and

[38] Available at: http://chbrp.com/analysis_methodology/medical_effectiveness_analysis.php.

- Insufficient evidence.

A grade of *clear and convincing evidence* indicates that there are multiple studies of a treatment and that the large majority of studies are of high quality and consistently find that the treatment is either effective or not effective.

A grade of *preponderance of evidence* indicates that the majority of the studies reviewed are consistent in their findings that treatment is either effective or not effective.

A grade of *limited evidence* indicates that the studies had limited generalizability to the population of interest and/or the studies had a fatal flaw in research design or implementation.

A grade of *inconclusive evidence* indicates that although some studies included in the medical effectiveness review find that a treatment is effective, a similar number of studies of equal quality suggest the treatment is not effective.

A grade of *insufficient evidence* indicates that there is not enough evidence available to know whether or not a treatment is effective, either because there are too few studies of the treatment or because the available studies are not of high quality. It does not indicate that a treatment is not effective.

Search Terms (* indicates truncation of word stem)

Adherence

Remission

Survival

Progression

Mortality

Optune

Tumor Treatment Fields

Tumor-Treatment Fields

Tumor Treating Fields

Tumor-Treating Fields

TTF

NovoTTF

APPENDIX C COST IMPACT ANALYSIS: DATA SOURCES, CAVEATS, AND ASSUMPTIONS

The cost analysis in this report was prepared by the members of the cost team, which consists of CHBRP task force members and contributors from the University of California, Los Angeles, and the University of California, Davis, as well as the contracted actuarial firm, Milliman, Inc. (Milliman).[39]

Information on the generally used data sources and estimation methods, as well as caveats and assumptions generally applicable to CHBRP's cost impact analyses are available on CHBRP's website.[40]

This appendix describes any analysis-specific data sources, estimation methods, caveats, and assumptions used in preparing this cost impact analysis.

Analysis Specific Caveats and Assumptions

This subsection discusses the caveats and assumptions relevant specifically to an analysis of SB 746.

CHBRP projects that SB 746:

- Would not impact any form of cost sharing, such as deductibles, copayments, and coinsurance;
- Would not affect plan or insurer methods of utilization management that may impact the coverage of medical treatments between baseline and postmandate periods, such as use of prior authorization requirements and review for medical necessity.

The following is a description of methodology and assumptions used to develop the estimates of cost impacts:

- The definition of "anticancer medical device" provided in the text of SB 746 was determined to be applicable at this time to a single device, Novocure's Optune®, for the treatment of GBM. This is consistent with the bill author's stated intent. While CHBRP is aware of other anticancer medical devices in the product pipeline, none are expected to become available within the timeline of this analysis.
- Optune® is identified by two Healthcare Common Procedure Coding System (HCPCS) codes: E0766 (new unit) and A4555 (replacement unit). Monthly rental fees for Optune® include all associated maintenance, parts, and services.
- Milliman extracted claims data for these codes from Milliman's 2016 Consolidated Health Cost Guidelines™ Sources Database (CHSD) and the 2016 MarketScan® Commercial Claims and Encounters Databases. These data were used to develop baseline cost-sharing assumptions for the Optune® device. The claims data are summarized in Table 6.

[39] CHBRP's authorizing statute, available at www.chbrp.org/docs/authorizing_statute.pdf, requires that CHBRP use a certified actuary or "other person with relevant knowledge and expertise" to determine financial impact.
[40] See *2019 Cost Impact Analyses: Data Sources, Caveats, and Assumptions*, available at www.chbrp.org/analysis_methodology/cost_impact_analysis.php.

Table 6. Optune® Utilization and Cost (2016 CHSD and MarketScan)

		Distinct Users	Total Utilization	Average Billed	Average Allowed	Average Paid	Average Patient Pay
Optune®	29	105	$21,000.00	$18,624.13	$18,138.79	$485.34	

- CHBRP did not include either offsets or costs of additional services associated with the use of the Optune® device.
- CHBRP relied upon the carrier surveys to determine existing coverage of Optune®. All respondents to the survey indicated that Optune® is currently covered, although some noted that coverage is subject to a determination of medical necessity or requires preauthorization.
- Per-unit cost is $21,000 per user per month, which includes component parts, services, and supplies necessary for the effective use of the device (Topfer and Farrah, 2018). (This matches claims data).
- The average length of use of Optune® is 5.2 months per user (Topfer and Farrah, 2018).
- The incidence rate for GBM in the population included in the CHBRP analysis is estimated from the incidence rate by age band provided in Ostrom et al. (2018) applied to the age distribution of the CHBRP population. The incidence rate estimate excludes any occurrence of GBM in members below the age of 18, as they would not be candidates for use of the Optune® device.
- For patients with a primary diagnosis of GBM, 30% were informed about TTFields (Optune®) based on a published study.
- Acceptance rate among these informed patients was 36% (Onken et al., 2018).
- CHBRP assumed 0% cost trend and 0% utilization trend for the baseline projection.
- CHBRP assumed a 10% one-time increase in utilization postmandate due to increased awareness and acceptance of the device.

Determining Public Demand for the Proposed Mandate

This subsection discusses public demand for the benefits SB 746 would mandate. Considering the criteria specified by CHBRP's authorizing statute, CHBRP reviews public demand for benefits relevant to a proposed mandate in two ways. CHBRP:

- Considers the bargaining history of organized labor; and
- Compares the benefits provided by self-insured health plans or policies (which are not regulated by the DMHC or CDI and therefore not subject to state-level mandates) with the benefits that are provided by plans or policies that would be subject to the mandate.

On the basis of conversations with the largest collective bargaining agents in California, CHBRP concluded that unions currently do not include cost-sharing arrangements for anticancer medical devices. In general, unions negotiate for broader contract provisions such as coverage for dependents, premiums, deductibles, and broad coinsurance levels. Among publicly funded self-insured health insurance policies, the preferred provider organization (PPO) plans offered by CalPERS currently have the largest number of

enrollees. The CalPERS PPOs currently provide benefit coverage similar to what is available through group health insurance plans and policies that would be subject to the mandate.

To further investigate public demand, CHBRP used a bill-specific coverage survey to ask carriers who act as third-party administrators for (non-CalPERS) self-insured group health insurance programs whether the relevant benefit coverage differed from what is offered in group market plans or policies that would be subject to the mandate. The responses indicated that there were no substantive differences.

Second Year Impacts on Benefit Coverage, Utilization, and Cost

As displayed in Table 7, the second year impacts of SB 746 would be substantially the same as the impacts in the first year (see Table 1).

Table 7. SB 746 Impacts on Benefit Coverage, Utilization, and Cost, 2021

	Baseline	Postmandate	Increase/ Decrease	Percentage Change
Benefit coverage				
Total enrollees with health insurance subject to state benefit mandates (a)	24,395,000	24,395,000	0	0%
Total enrollees with health insurance subject to SB 746	24,395,000	24,395,000	0	0%
Percentage of enrollees with coverage for mandated benefit	91%	100%	9%	10%
Utilization and unit cost				
Utilization per 1,000	0.012	0.013	0.001	10%
Unit cost per month	$18,624	$18,624	0	0%
Number of enrollees using mandated benefit	55	61	6	11%
Average cost per enrollee using anticancer medical devices	96,845	96,845	0	0%
Expenditures				
Premiums by payer				
Private employers for group insurance	$90,700,422,000	$90,700,797,000	$375,000	0.0004%
CalPERS HMO employer expenditures (c) (b)	$3,234,903,000	$3,234,914,000	$11,000	0.0003%
Medi-Cal Managed Care Plan expenditures	$29,186,401,000	$29,186,578,000	$177,000	0.0006%
Enrollees with individually purchased insurance	$13,111,153,000	$13,111,225,000	$72,000	0.0005%
Enrollees with group insurance, CalPERS HMOs, Covered California, and Medi-Cal Managed Care (c)	$15,255,718,000	$15,255,795,000	$77,000	0.0005%
Enrollee expenses				
For covered benefits (deductibles, copayments, etc.)	$15,636,259,000	$15,636,191,000	-$68,000	-0.0004%
For noncovered benefits (d) (e)	$0	$0	$0	0.00%
Total expenditures	$167,124,856,000	$167,125,500,000	$644,000	0.0004%

Source: California Health Benefits Review Program, 2019.

Notes: (a) Enrollees in plans and policies regulated by DMHC or CDI aged 0 to 64 years as well as enrollees 65 years or older in employer-sponsored health insurance. This group includes commercial enrollees (including those associated with Covered California or CalPERS) and Medi-Cal beneficiaries enrolled in DMHC-regulated plans.[41]

(b) Approximately 56.17% of CalPERS enrollees in DMHC-regulated plans are state retirees, state employees, or their dependents. About one in five (20.5%) of these enrollees has a pharmacy benefit not subject to DMHC.[42] CHBRP has projected no impact for those enrollees. However, CalPERS could, postmandate, require equivalent coverage for all its members (which could increase the total impact on CalPERS).

(c) Enrollee premium expenditures include contributions by employees to employer-sponsored health insurance, health insurance purchased through Covered California, and contributions to Medi-Cal Managed Care.

(d) Includes only expenses paid directly by enrollees (or other sources) to providers for services related to the mandated benefit that are not currently covered by insurance. This only includes those expenses that would be newly covered postmandate. Other components of expenditures in this table include all health care services covered by insurance.

(e) Although enrollees with newly compliant benefit coverage may have paid for some treatments before SB 746, CHBRP cannot estimate the frequency with which such situations may have occurred and therefore cannot estimate the related expense. Postmandate, such expenses would be eliminated, though enrollees with newly compliant benefit coverage might, postmandate, pay for some treatments for which coverage is denied (through utilization management review), as some enrollees who always had compliant benefit coverage may have done and may continue to do, postmandate.

Key: CalPERS = California Public Employees' Retirement System; CDI = California Department of Insurance; DMHC = Department of Managed Health Care; HMO = Health Maintenance Organizations

[41] For more detail, see *Estimates of Sources of Health Insurance in California*, available at http://chbrp.com/analysis_methodology/cost_impact_analysis.php.
[42] For more detail, see *Estimates of Pharmacy Benefit Coverage*, available at http://chbrp.com/analysis_methodology/cost_impact_analysis.php.

APPENDIX D INFORMATION SUBMITTED BY OUTSIDE PARTIES

In accordance with the California Health Benefits Review Program (CHBRP) policy to analyze information submitted by outside parties during the first 2 weeks of the CHBRP review, the following parties chose to submit information.

The following information was submitted by the office of Senator Patricia C. Bates in March 2019.

Bates, Senator Patricia C. Fact Sheet - SB 746: Treatment Coverage for Anticancer Medical Devices. Office of Senator Patricia C. Bates. 2019 Mar 1.

Submitted information is available upon request. For information on the processes for submitting information to CHBRP for review and consideration please visit www.chbrp.org/requests.html.

REFERENCES

Albain KS, Unger JM, Crowley JJ, Coltman CA Jr., Hershman DL. Racial disparities in cancer survival among randomized clinical trials patients of the southwest oncology group. *Journal of the National Cancer Institute.* 2009;101:984-992.

American Cancer Society (ACS). 5-year relative survival, 2008-2014. Based on National Cancer Institute Data, 2018. Available at: https://cancerstatisticscenter.cancer.org/#!/data-analysis/SurvivalByStage. Accessed March 20, 2019.

American Cancer Society (ACS). Cancer Statistics Center: California. Available at: https://cancerstatisticscenter.cancer.org/?_ga=2.217422358.1212783208.1552521849-84744138.1541805237#!/state/California. Accessed March 19, 2019.

American Cancer Society (ACS). Survival rates for selected brain and spinal cord tumors. November 7, 2017. Available at: https://www.cancer.org/cancer/brain-spinal-cord-tumors-adults/detection-diagnosis-staging/survival-rates.html. Accessed March 19, 2019.

Bernard-Arnoux F, Lamure M, Ducray F, Aulagner G, Honnorat J, Armoiry X. The cost-effectiveness of tumor-treating fields therapy in patients with newly diagnosed glioblastoma. *Neuro-Oncology*. 2016;18(8):1129-1136.

Bohn A, Braley A, de la Vega PR, Zevallos JC, Barengo NC. The association between race and survival in glioblastoma patients in the US: A retrospective cohort study. *PloS One.* 2018;21:13(6):e0198581.

California Cancer Registry (CCR). California Cancer Facts and Figures, 2017. Available at: https://www.cancer.org/content/dam/cancer-org/online-documents/en/pdf/reports/california-facts-figures-2017.pdf. Accessed March 19, 2019.

California Department of Public Health (CDPH). Center for Health Statistics and Informatics Death Data Trend Summary: Premature Mortality Trends 2000-2007. June 2009. Available at: http://www.cdph.ca.gov/programs/ohir/Pages/YPLL2007Main.aspx. Accessed December 2011.

Centers for Disease Control and Prevention. NCHHSTP Social Determinants of Health. Frequently Asked Questions. Page last reviewed: March 10, 2014. Available at: http://www.cdc.gov/nchhstp/socialdeterminants/faq.html. Accessed August 27, 2015.

Cox D. Premature Mortality in California, 2004. Center for Health Statistics. December 2006. Available at: http://www.cdph.ca.gov/pubsforms/Pubs/OHIRprematuremortality2004.pdf. Accessed November 2011.

Dressler EV, Liu M, Garcia CR, Dolecek TA, Pittman T, Huang B, Villano JL. Patterns and disparities of care in glioblastoma. *Neuro-Oncology Practice*. 2018;6(1):37-46.

Drexell Hunter Boggs. A Pilot and Feasibility Trial to Determine the Rate of the Brain Relapse in Small Cell Lung Cancer (SCLC) Patients With Brain Metastases Treated With Stereotactic Radiosurgery (SRS) Followed by Tumor Treating Fields (TTF). NLM identifier: NCT03488472. Available at: https://clinicaltrials.gov/ct2/show/NCT03488472?term=TTFields&cond=Brain+Metastases&rank=3. Accessed April 1, 2019.

Gittleman H, Boscia A, Ostrom QT, Truitt G, Fritz Y, Kruchko C, Barnholtz-Sloan JS. Survivorship in adults with malignant brain and other central nervous system tumor from 2000–2014. *Neuro-Oncology*. 2018;20(suppl_7):vii6-16.

Green AL, Mulcahy Levy JM, Vibhakar R, et al. Tumor treating fields in pediatric high-grade glioma. *Child's Nervous System : ChNS : Official Journal of the International Society for Pediatric Neurosurgery*. 2017;33(7):1043-1045.

Kanner AA, Wong ET, Villano JL, Ram Z. Post Hoc analyses of intention-to-treat population in phase III comparison of NovoTTF-100A system versus best physician's choice chemotherapy. *Seminars in Oncology*. 2014;41 Suppl 6:S25-34.

Kesari S, Ram Z. Tumor-treating fields plus chemotherapy versus chemotherapy alone for glioblastoma at first recurrence: a post hoc analysis of the EF-14 trial. *CNS Oncology*. 2017;6(3):185-193.

Killion JA, Giddings BM, Chen Y, et al. Cancer in California, 1988-2015. Sacramento, CA: California Department of Public Health, Chronic Disease Surveillance and Research Branch, April 2018. Available at: https://www.ccrcal.org/retrieve-data/data-for-the-public/cancer-statistics-and-reports/. Accessed March 19, 2019.

Kinzel A, Ambrogi M, Varshaver M, Kirson ED. Tumor treating fields for glioblastoma treatment: patient satisfaction and compliance with the second-generation Optune® system. *Clinical Medicine Insights: Oncology*. 2019;13:1179554918825449.

Mandel J, Youssef M, Nam JY, Wu J, Liu DD, Bondy M, De Groot J. Effect of Health Disparities on Overall Survival of Patients with Glioblastoma. *Journal of Neuro-Oncology*. 2019.

Meropol NJ, Schulman KA. Cost of cancer care: Issues and implications. *Journal of Clinical Oncology*. 2007;25:180-186.

Mrugala MM, Engelhard HH, Dinh Tran D, et al. Clinical practice experience with NovoTTF-100A system for glioblastoma: The Patient Registry Dataset (PRiDe). *Seminars in Oncology*. 2014;41 Suppl 6:S4-s13.

National Cancer Institute (NCI). Understanding Cancer: Cancer Disparities. October 2016. Available at: www.cancer.gov/about-cancer/understanding/disparities. Accessed April 19, 2019.

National Comprehensive Cancer Network (NCCN). Central Nervous System Cancers (Version 1.2019). Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed April 16, 2019.

Novocure Ltd. Pivotal, Open-label, Randomized Study of Radiosurgery With or Without Tumor Treating Fields (TTFields) (150kHz) for 1-10 Brain Metastases From Non-small Cell Lung Cancer (NSCLC). NLM identifier: NCT02831959. Available at: https://clinicaltrials.gov/ct2/show/NCT02831959?term=TTFields&cond=Brain+Metastases&rank=1. Accessed April 1, 2019.

Office of Disease Prevention and Health Promotion. Healthy People 2020: Social Determinants of Health. Available at: http://www.healthypeople.gov/2020/topics-objectives/topic/socialdeterminantshealth/addressing-determinants. Accessed February 16, 2016.

Onken J, Staub-Bartelt F, Vajkoczy P, Misch M. Acceptance and compliance of TTFields treatment among high grade glioma patients. *Journal of Neuro-Oncology*. 2018;139(1):177-84.

Ostrom QT, Gittleman H, Liao P, Vecchione-Koval T, Wolinsky Y, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2010–2014. *Neuro-Oncology*. 2017;19(suppl_5):v1-88

Pless M, Droege C, von Moos R, Salzberg M, Betticher D. A phase I/II trial of Tumor Treating Fields (TTFields) therapy in combination with pemetrexed for advanced non-small cell lung cancer. *Lung Cancer* (Amsterdam, Netherlands). 2013;81(3):445-450.

Rivera F, Benavides M, Gallego J, Guillen-Ponce C, Lopez-Martin J, Kung M. Tumor treating fields in combination with gemcitabine or gemcitabine plus nab-paclitaxel in pancreatic cancer: Results of the PANOVA phase 2 study. *Pancreatology: Official Journal of the International Association of Pancreatology* (IAP). 2019;19(1):64-72.

Rouse C, Gittleman H, Ostrom QT, Kruchko C, Barnholtz-Sloan JS. Years of potential life lost for brain and CNS tumors relative to other cancers in adults in the United States, 2010. *Neuro-Oncology*. 2015;18(1):70-7.

Sloane D. Cancer epidemiology in the United States: racial, social, and economic factors. *Methods in Molecular Biology*. 2009;471:65-83.

Stupp R, Taillibert S, Kanner A, et al. Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial. *JAMA*. 2017;318(23):2306-2316.

Stupp R, Taillibert S, Kanner AA, et al. Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial. *JAMA*. 2015;314(23):2535-2543.

Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. *European Journal of Cancer* (Oxford, England: 1990). 2012;48(14):2192-2202.

Taphoorn MJB, Dirven L, Kanner AA, et al. Influence of Treatment With Tumor-Treating Fields on Health-Related Quality of Life of Patients With Newly Diagnosed Glioblastoma: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Oncology*. 2018;4(4):495-504.

Tehranifar P, Neugut AI, Phelan JC, et al. Medical advances and racial/ethnic disparities in cancer survival. *Cancer Epidemiology, Biomarkers & Prevention*. 2009;18:27.

Toms SA, Kim CY, Nicholas G, Ram Z. Increased compliance with tumor treating fields therapy is prognostic for improved survival in the treatment of glioblastoma: a subgroup analysis of the EF-14 phase III trial. *Journal of Neuro-Oncology*. 2019;141(2):467-473.

Topfer LA, Farrah K. Alternating Electric Fields ("Tumour-Treating Fields") for the Treatment of Glioblastoma. *CADTH Issues in Emerging Health Technologies*. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; Copyright (c) CADTH 2018.

Vergote I, von Moos R, Manso L, Van Nieuwenhuysen E, Concin N, Sessa C. Tumor Treating Fields in combination with paclitaxel in recurrent ovarian carcinoma: Results of the INNOVATE pilot study. *Gynecologic Oncology*. 2018;150(3):471-477.

Ward E, Jemal A, Cokkinides V, et al. Cancer disparities by race/ethnicity and socioeconomic status. CA: *A Cancer Journal for Clinicians*. 2004;54:78-93.

Wyatt R, Laderman M, Botwinick L, Mate K, Whittington J. *Achieving Health Equity: A Guide for Health Care Organizations*. IHI White Paper. Cambridge, Massachusetts: Institute for Healthcare Improvement; 2016. (Available at ihi.org)

Zhu JJ, Demireva P, Kanner AA, et al. Health-related quality of life, cognitive screening, and functional status in a randomized phase III trial (EF-14) of tumor treating fields with temozolomide compared to temozolomide alone in newly diagnosed glioblastoma. *Journal of Neuro-Oncology*. 2017;135(3):545-552.

CALIFORNIA HEALTH BENEFITS REVIEW PROGRAM COMMITTEES AND STAFF

A group of faculty, researchers, and staff complete the analysis that informs California Health Benefits Review Program (CHBRP) reports. The CHBRP **Faculty Task Force** comprises rotating senior faculty from University of California (UC) campuses. In addition to these representatives, there are other ongoing researchers and analysts who are **Task Force Contributors** to CHBRP from UC that conduct much of the analysis. The **CHBRP staff** coordinates the efforts of the Faculty Task Force, works with Task Force members in preparing parts of the analysis, and manages all external communications, including those with the California Legislature. As required by CHBRP's authorizing legislation, UC contracts with a certified actuary, **Milliman**, to assist in assessing the financial impact of each legislative proposal mandating or repealing a health insurance benefit.

The **National Advisory Council** provides expert reviews of draft analyses and offers general guidance on the program to CHBRP staff and the Faculty Task Force. CHBRP is grateful for the valuable assistance of its National Advisory Council. CHBRP assumes full responsibility for the report and the accuracy of its contents.

Faculty Task Force

Janet Coffman, MA, MPP, PhD, *Vice Chair for Medical Effectiveness*, University of California, San Francisco
Sylvia Guendelman, PhD, LCSW, University of California, Berkeley
Gerald Kominski, PhD, University of California, Los Angeles
Sara McMenamin, PhD, *Vice Chair for Medical Effectiveness and Public Health*, University of California, San Diego
Joy Melnikow, MD, MPH, *Vice Chair for Public Health*, University of California, Davis
Jack Needleman, PhD, University of California, Los Angeles
Ninez Ponce, PhD, University of California, Los Angeles
Nadereh Pourat, PhD, *Vice Chair for Cost*, University of California, Los Angeles
Marilyn Stebbins, PharmD, University of California, San Francisco
Ed Yelin, PhD, Professor Emeritus, University of California, San Francisco

Task Force Contributors

Danielle Casteel, MA, University of California, San Diego
Shana Charles, PhD, MPP, University of California, Los Angeles, and California State University, Fullerton
Shauna Durbin, MPH, University of California, Davis
Margaret Fix, MPH, University of California, San Francisco
Sarah Hiller, MA, University of California, San Diego
Naomi Hillery, MPH, University of California, San Diego
Jeffrey Hoch, PhD, University of California, Davis
Michelle Ko, MD, PhD, University of California, Davis
Connie Kwong, University of California, San Francisco
Kevin Lee, PhD Candidate, University of California, Berkeley
Elizabeth Magnan, MD, PhD, University of California, Davis
Ying-Ying Meng, PhD, University of California, Los Angeles
Jacqueline Miller, University of California, San Francisco
Dominique Ritley, MPH, University of California, Davis
Dylan Roby, PhD, University of California, Los Angeles, and

California Health Benefits Review Program
MC 3116
Berkeley, CA 94720-3116
info@chbrp.org
www.chbrp.org
(510) 664-5306

*Karen Shore, PhD, is an Independent Contractor with whom CHBRP works to support legislative analyses and other special projects on a contractual basis.

CHBRP is an independent program administered and housed by the University of California, Berkeley, in the Office of the Vice Chancellor for Research.

CHBRP gratefully acknowledges the efforts of the team contributing to this analysis:

Janet Coffman, MA, MPP, PhD, and Chris Toretsky, MPH of the University of California, San Francisco, prepared the medical effectiveness analysis. Stephen L. Clancy, MLS, AHIP, of the University of California, Irvine, conducted the literature search. Sara McMenamin, PhD, and Sara Yoeun, of the University of California, San Diego, prepared the public health impact analysis. Ying-Ying Meng, PhD of the University of California, Los Angeles, prepared the cost impact analysis. Daniel Henry, FSA, MAAA, of Milliman, provided actuarial analysis. Mekhail Anwar, MD, PhD, Assistant Professor, Department of Radiation Oncology, University of California, San Francisco, provided technical assistance with the literature search and expert input on the analytic approach. Karen Shore, PhD, CHBRP contractor prepared the Policy Context and synthesized the individual sections into a single report. A subcommittee of CHBRP's National Advisory Council (see final pages of this report) and a member of the CHBRP Faculty Task Force, Sylvia Guendelman, PhD, LCSW, of the University of California, Berkeley, reviewed the analysis for its accuracy, completeness, clarity, and responsiveness to the Legislature's request.

CHBRP assumes full responsibility for the report and the accuracy of its contents. All CHBRP bill analyses and other publications are available at www.chbrp.org.

Garen Corbett, MS
Director

Please direct any questions concerning this document to: California Health Benefits Review Program; MC 3116; Berkeley, CA 94720-3116, info@chbrp.org, or www.chbrp.org